Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

49th Meeting
20-22 February 2007

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACSPA	Australian Consumer and Specialty Products Association
ADEC	Australian Drug Evaluation Committee
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHMAC	Australian Health Ministers' Advisory Council
APMF	Australian Paint Manufacturers Federation
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
BAN	British Approved Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments

CPAS	Chemical Product Assessment Section
CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonisation
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
DAP	Drafting Advisory Panel
DSEB	Drug Safety and Evaluation Branch
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
HCN	Health Communication Network
INN	International Non-proprietary Name
ISO	International Standards Organization
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance

LC_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
MCC	Medicines Classification Committee
MEC	Medicines Evaluation Committee
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
NPMB	Non-Prescription Medicines Branch
NZ	New Zealand
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety
ODBT	Office of Devices, Blood and Tissues
OOS	Out of Session
OTC	Over the Counter
PACIA	Plastics And Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee

PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
RFI	Restricted Flow Insert
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1. PRELIMINARY MATTERS

1.7 PROCEDURAL MATTERS

1.7.1 OPERATIONS/POLICIES OF THE COMMITTEE

1.7.1.1 [ITEM DELETED]

1.7.1.2 GUIDELINES FOR CONFIDENTIAL INFORMATION - MEDICINES

PURPOSE

The Committee considered foreshadowed changes to the NDPSC guidelines regarding confidential information in medicines submissions.

BACKGROUND

The October 2002 NDPSC Meeting agreed to edit the NDPSC guidelines to remove outdated or incorrect material (including Chapter 5 – *Guidelines for use of Confidential Information*). The Committee flagged that the NDPSC Guidelines Working Party may need to be reconstituted following the Galbally report to re-write the guidelines. However, re-writing of the guidelines was not progressed due to work being undertaken with the implementation of Galbally Recommendation 7 (splitting of the NDPSC into two separate committees) as part of the establishment of the ANZTPA.

The October 2005 NDPSC Meeting considered stakeholder concern about the release of "confidential" information. Members agreed that no changes to the Secretariat's editing of the Record of Reasons were warranted at that time and confirmed the current practice of the Secretariat as appropriate. The Committee further agreed to reconsider this issue at the February 2006 NDPSC Meeting as an opportunity existed to progress some of the moves towards further transparency before the trans-Tasman arrangements come into force.

The February 2006 NDPSC Meeting referred this issue to NCCTG. The June 2006 NDPSC Meeting noted the May 2006 NCCTG's consideration of this issue and agreed to foreshadow consideration of changes to the operational requirements for the NDPSC regarding CIC and transparency of information for medicines scheduling. Comments were particularly invited from stakeholders on the NCCTG's proposed starting point for consultation and on defining any additional types of information over which stakeholders sought confidentiality.

The October 2006 NDPSC Meeting:

- Agreed to foreshadow consideration at the February 2007 NDPSC Meeting of a proposed entry for Chapter 5 of the NDPSC guidelines.

- Agreed that the proposed entry would apply to medicines only.
- Agreed to refer the proposed guideline changes to NCCTG for consideration and approval.
- Agreed that no changes to the Secretariat's editing of the Record of Reasons were warranted at this time and confirmed the current practice of the Secretariat as appropriate.

DISCUSSION

The November 2006 NCCTG Meeting gave consideration to the foreshadowed NDPSC guideline changes. The Committee particularly noted that:

- The NCCTG members endorsed the proposed new Chapter 5 entry to provide guidance to stakeholders around the issue of medicines information released to the public in the NDPSC's Record of Reasons and pre-meeting gazette notice.
- It was highlighted that sponsor name and product name were mandatory label information and so not obviously information that should be treated as commercial-in-confidence. Whether the sponsor name and product name should be treated as commercial-in-confidence could become part of the Scheduling Framework Policy consultation.

Members also noted the following from pre-meeting comments:

XXXX:

- XXXX was pleased to note that the current editing of the Record of Reason by the Secretariat would remain unchanged.
- As noted in previous comments, XXXX considered review of processes surrounding transparency a positive move. However, concerns still remained on to this issue, and XXXX re-iterating its previous comments in relation to this matter. Therefore, XXXX opposed any change to the current arrangements until the ANZTPA scheduling framework is finalised.

XXXX:

- It is XXXX firm view that the pre-meeting gazette notice must include details of the substance or issue under consideration, including the intent of any scheduling/rescheduling proposals. XXXX did not believe it was acceptable that public submissions could be called without details of proposals being released in full. For example, "consideration of scheduling" is not adequate unless it relates to an agenda item that can be referenced back to the Record of Reasons. In addition, XXXX believed that information such as strength and dose form must also be included together with the substance name.

Currently the Record of Reasons is produced from the Ratified Minutes through deletion of material considered by the Secretariat to be commercially sensitive (i.e., formulation detail, manufacturing method, sponsor name, product name, sales information), details from the evaluation reports for new agvet products and extracts from the ADEC minutes. This process was often subjective and the onus for identifying confidential information had fallen on the Secretariat. The Record of Reasons also usually excluded items such as Committee procedures, information items, policy items under development and Members reports.

The current Record of Reasons, with its increased details and information compared to historical standards, was introduced in part because of pressure from stakeholders for increased transparency about the reasons for a decision. The Secretariat, in including information in the Record of Reasons, advised that it was being pushed by two agenda:

- drive for transparency about the basis for NDPSC decisions. The opportunity to comment on a decision loses meaning if stakeholders cannot access the details of the reasons behind a decision.
- continuing strong pressure on the Secretariat by some stakeholders to have as little information about their product(s) as possible available to the public.

The Secretariat also advised that the above agenda arose with the issue of the pre-meeting gazette notice. While in general there was a desire for more transparency in the gazette notices, the individual applicants were often reluctant to have additional information in the gazette. The Secretariat had attempted to encourage applicants to include a proposed gazettal notice in their submission but this did not generally occur.

Members recalled that the June 2006 NDPSC Meeting noted that the NCCTG:

- affirmed that it was anticipated that the new Medicines Scheduling Committee would release more information publicly than the NDPSC currently released.
- considered that the starting point for consultation with industry stakeholders should be that the only information that should be routinely withheld from public release was CIC information (i.e., formulation detail, manufacturing method, sponsor name, product name and sales information).
- particularly considered that the existence of an application or the identity of a substance that was the subject of a rescheduling application was not CIC information.
- suggested that the Committee should be prepared to work with industry groups on defining any additional types of information over which industry stakeholders sought confidentiality.
- noted that commercial and market advantage could be gained from the limited release of information from the NDPSC. Once guidelines were in place for wider release of information, applicants would be able to adjust the timing of the lodgement of their submissions to take account of the policies on public release of information.

and that the NCCTG therefore:

- supported a greater level of transparency in the release of information, consistent with the requirements of CIC material and public need.
- recommended that the NDPSC consult with industry stakeholders to define the level of transparency that was appropriate.
- recommended that stakeholder responses that were submitted in relation to the consultation on the Draft Model be considered in reviewing the NDPSC guidelines on release of information.

Members also recalled advice to the June 2006 NDPSC Meeting that the XXXX did not support inclusion of information from agvet evaluations in the Record of Reasons. A Member therefore suggested that the Committee defer consideration of the confidential information issue for the poisons side of scheduling, noting that APVMA had specific legislative requirements that may impede development of a consistent position. The Committee agreed that it was appropriate to separate consideration of confidentiality for medicines scheduling from poisons scheduling given that there will shortly be different operational requirements.

Members also noted the following advice provided by XXXX to the October 2006 NDPSC Meeting:

- A key issue in the 2005 consultation on the Draft Model raised by stakeholders was the proposed arrangements for CIC material. Members particularly noted:
  - The draft guidelines regarded sales data, details of manufacturing processes and formulation details as confidential information.
  - Applicants would be required to identify and justify any further claims of confidentiality based on relevant freedom of information legislation and intellectual property rights.
- It was also noted that several submissions called for the scope of material accepted as being CIC to either be expanded, or for a process to be built in whereby the applicant would have an opportunity to review the material to be published on the website, prior to release.
- In considering these comments NCCTG agreed that while only minimal information should generally be accepted as CIC, provision should be made for further information to be treated as CIC on a case by case basis.
- The XXXX felt that the proposed guidelines were a positive move for transparency. XXXX noted that progress in this area could lead to the evolution of a workable model for the new Medicines Schedule Committee. XXXX thought that the Committee had a great opportunity to develop practices, in partnership with industry, that were mutually agreeable and which contained no surprises.

The October 2006 NDPSC Meeting also noted the following comments from Members:

- XXXX advised that industry appreciated the clarity of NCCTG's proposed starting point and the provision allowing justification of additional information as CIC on a case-by-case basis. It was asserted that industry was comfortable with the Committee's proposed guidelines on medicines CIC information. Another Member noted that case-by-case consideration, while not an insignificant undertaking, has value as it would also allow an appropriate evolution of the guidelines.
- Member noted that the Committee would need to try and work in parallel with the development of this issue for ANZTPA. It was noted that while the Committee could not get too far ahead of ANZTPA it still wanted to progress and improve the Secretariat's operations and efficiencies. The Committee agreed that it was therefore important that the Secretariat and JAEG work closely together on these issues.

OUTCOME

The Committee:

- noted that separate guidelines were being developed for CIC information under ANZTPA but agreed that this did not restrict the Members from updating the guidelines for the current Committee.
- confirmed the foreshadowed new entry for Chapter 5 of the NDPSC Guidelines.
- confirmed that this entry applied to medicines only.

NDPSC Guidelines – New entry for Chapter 5.

MEDICINES INFORMATION

Medicines Information released to the public in the Record of Reasons

The only information that will be routinely withheld from public release is commercial-in-confidence information (i.e., formulation detail, manufacturing method, sponsor name, product name and sales information).

The applicant must provide a written justification for any other material the applicant wishes to be treated as commercially sensitive. The nominated contact person will be notified if this justification has not been upheld prior to the release of the Record of Reasons.

Applicants should note that the existence of an application or the identity of a substance that is the subject of a rescheduling application is not commercial-in-confidence information.

In addition, items such as Committee procedures, information items, policy items being developed and Members reports will not usually be included in the Record of Reasons.

Medicines Information released to the public in the pre-meeting gazette notice.

The pre-meeting gazette notice may include details of the substance or issue under consideration, including the intent of any scheduling/rescheduling proposals. Applicant's should include a proposed gazettal notice in their submission, including a justification if the applicant wishes information withheld from the pre-meeting gazette notice.

1.7.1.3 DERIVATIVE USAGE IN THE SUSDP

PURPOSE

The Committee considered the usage of the term "derivative" in the SUSDP, including the inclusion a new paragraph under the "Principles of Scheduling" section of the SUSDP.

BACKGROUND

At the May 1995 NDPSC Meeting, during discussion of retinyl palmitate, it was noted that because of the inclusion of then sub-paragraph 76(7) in the SUSDP, it could be interpreted that esters and ethers were not included as derivatives of poisons other than those included in Schedule 8. The Drafting Advisory Panel was requested to redraft the section to clarify the meaning. The August 1995 NDPSC Meeting therefore agreed to "every salt, active principle or derivative of the poison, including esters and ethers, and every salt of such an active principle or derivative".

The May 1996 NDPSC Meeting considered correspondence which illustrated that there may be some ambiguity in how the term "derivative" may be interpreted for scheduling purposes. Discussion remained focused, however, on a number of specific substances and did not address the broader usage of derivative in the SUSDP.

The June 2006 NDPSC Meeting considered a scheduling submission regarding potassium azeloyl diglycinate (PAD). The Committee noted that there was no definition of derivative in the SUSDP but generally agreed that in this instance it was appropriate to consider PAD as a separate substance (rather than a derivative of azelaic acid) as it had different biological properties and a different use. However, Members remained concerned by the lack of clarity about what was meant by derivative in Part 1, Paragraph (2)(c) and agreed to foreshadow consideration at the October 2006 NDPSC Meeting of the usage of "derivative" in the SUSDP, including the possibility of creating a definition.

The October 2006 NDPSC Meeting agreed to foreshadow consideration at the February 2007 NDPSC Meeting of a draft paragraph for inclusion under the "Principles of Scheduling" section of the SUSDP to clarify the intent of the Committee in using

derivative in the context of a schedule entry. A Committee working party, in consultation with the Secretariat, developed a draft paragraph out of session which was included in the October 2006 NDPSC minutes.

DISCUSSION

The Committee was advised that the following pre-meeting comments were received in response to the foreshadowed proposal:

XXXX:

- Recommended that the Committee seek legal advice as there were cases in patent and criminal law where the word "derivative", in a chemical context, has been interpreted. Given that the SUSDP is adopted in whole or in part by State and Territory criminal law, it is important that any definition used in the SUSDP is supported by legal authority.
  [The Members noted that this comment seemed to relate to the issue of a definition for derivative rather than the guidance on derivative which was being considered]

XXXX:

- XXXX did not object to the proposal on the basis that this outcome sought to achieve greater clarity and not to result in further scheduling or scheduling consideration of substances that may be derivatives.

XXXX:

- Noted an interest in this item. XXXX advised that it would also provide comment through XXXX.

The Committee recalled that a number of possible solutions to the derivative issue were considered at the October 2006 NDPSC Meeting. In discussing these possible solutions the Meeting noted the following:

- Members confirmed that they did not believe that there was currently a problem, and agreed that they had not mis-scheduled substances through the current application of derivative. This October Meeting's consideration of derivative was instead driven by a desire to increase transparency and provide clarity.
- A Member advocated leaving existing entries alone, and that entries only be revisited if an issue or concern arose, or a sponsor asked for a ruling. The Member was concerned about defining derivative and having retrospective, probably unintended, impact. The Members were advised that while the NZ Misuse of Drugs Act (MODA) used the term derivative the MODA did not have a definition. A Jurisdictional Member advised that they also used derivative in their MODA and would oppose removal of the term.

- A Member noted that for a derivative to be appropriately captured under a parent compounds schedule the derivative should not be more toxic than the parent. Higher toxicity should require a separate scheduling consideration.
- A Member noted that the usage of derivative was not a major concern for pharmaceuticals as each active went through the regulator who was able to refer such actives to the Committee if necessary. However, it was acknowledge that the derivatives issue could have a large impact on chemicals, particularly domestic chemicals.
- The Committee considered a proposed definition of derivative. A Member noted, however, that flexibility should be maintained. Without flexibility in the derivative usage the Member asserted that the Committee would be hard pressed to appropriately schedule a rapidly evolving class of substances.
- The Committee agreed that it was not appropriate to define derivative in the SUSDP as this concept was too complex for a prescriptive, inflexible, approach. Members instead agreed to include a paragraph under the "Principles of Scheduling" section of the SUSDP setting out the Committee's intent with regard to applying derivative to schedule entries. This paragraph would explain why the Committee was trying to capture certain substances as derivatives and what the Members want to convey or prevent. Members agreed that such a paragraph would be transparent and assist users of the SUSDP.
- A Member also suggested that a definition, while possibly useful as a guide to the evaluators, particularly OCS or NICNAS, would be too prescriptive and inflexible for inclusion in the SUSDP. Evaluators could, however, address some of the proposed elements in the definition if there was data to do so, and thus give the Committee information for deciding if there should be a limitation or specification on the application of derivative for a substance. The Member suggested that the Committee could ask evaluators that, when they provide their assessment, they specify (as best the data allows) whether derivatives should be allowed, or limited to either certain classes of derivate or to no derivatives. This would leave sufficient flexibility to deal with the diversity of substances that are scheduled.

Member's noted that post-meeting action from the October 2006 NDPSC Meeting had initiated the development of guidelines for evaluators to use when considering if there were any derivative issues for substances they are assessing.

DECISION 2007/49 - 1

The Committee agreed to amend the "Principles of Scheduling" section of the SUSDP to clarify the intent of the Committee in using derivative in the context of a schedule entry.

PRINCIPLES OF SCHEDULING - READING THE SCHEDULES - Amendment

Schedule entries have been designed to be as simple as possible while retaining readability, legal integrity and as much freedom from ambiguity and contradiction as possible. As a result they are expressed in a number of ways, though this number has been kept to a minimum. It is necessary to keep this variety of expression in mind when searching or interpreting Schedule entries.

Firstly, poisons are now scheduled individually using their approved names wherever practicable although exceptions are necessary in some cases. Some of those are mentioned overleaf. Older group entries are being revised and replaced by individual entries as time permits although in some of these cases a group term has also been retained to deal with any members of the group or class that may have escaped attention but should be scheduled.

Secondly, schedule entries have been expressed in either positive or negative terms and care must be taken to distinguish between the two different forms of expression. Thus, selenium is in Schedule 6 only when one of the clauses in this schedule entry applies, while fluorides are in Schedule 6 unless one of the exempting clauses applies.

Where exceptions are included in an entry these have been emphasised by printing the word "except" in bold type.

Where the schedule entries for a poison make a specific exclusion or exemption, the requirements of this Standard do not apply to that poison within the constraints of that exclusion or exemption although controls under other legislation such as pesticide registration may apply.

Where a poison has been included in more than one Schedule the principal entry, where practicable, has been included in the most restrictive Schedule with references to the other Schedule(s) involved.

It is important to remember that a Schedule entry includes preparations containing the poison in any concentration and all salts and derivatives of the poison unless it specifically states otherwise. (See Interpretation PART 1 [paragraph 1(2)]).

It is important to note that a substance is not classed as a derivative on the basis of a single, prescriptive set of criteria. Classification of a substance as a derivative of a Scheduled poison relies on a balanced consideration of factors to decide if a substance

has a similar nature (e.g. structurally, pharmacologically, toxicologically) to a Scheduled poison or is readily converted (either physically or chemically) to a Scheduled poison. However, a substance is only considered a derivative of a Scheduled poison if it is not individually listed elsewhere in the Schedules, or captured by a more restrictive group or class entry. Additionally, some entries specifically exclude derivatives. Once a substance is determined to be a derivative of a Scheduled poison, the same scheduling requirements as the Scheduled poison, including limits on access, supply and availability, will apply.

Finally, when using the Standard to determine the scheduling status of a poison it may be necessary to search each relevant Schedule as well as Appendices A, B and C and the Index. In this process if the poison is not found under its "approved name" it may be shown under a group term such as:

Group	Example
the parent acid of salts	"oxalic acid" to find sodium oxalate
the radical of a salt	"chromates" to find potassium chromate
the element	"arsenic" to find arsenic trioxide
a chemical group with similar toxicological or pharmacological activity	"hydrocarbons, liquid" to find kerosene
a pharmacological group	"anabolic steroidal agents" to find "androsterone"

1.8 NDPSC WORKING PARTIES

1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY

1.8.1.1 FORESHADOWED HARMONISATION PROPOSALS – HYALURONIDASE AND METHYL SALICYLATE

PURPOSE

The Committee considered the scheduling of hyaluronidase and methyl salicylate as foreshadowed at the October 2006 NDPSC Meeting.

BACKGROUND

The June 2006 TTHWP Meeting noted the completion of the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedules 2, 3, 4 and 8 and

equivalent NZ classifications, where available. The TTHWP considered each remaining unharmonised substance and agreed that the TTHWP's recommendations be included on the agenda of the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed the above recommendations and foreshadowed consideration of remaining unharmonised medicines at the October 2006 NDPSC Meeting to allow appropriate public consultation. The October 2006 NDPSC Meeting therefore considered a number of substances, including for methyl salicylate and hyaluronidase. Members agreed to foreshadow consideration of methyl salicylate and hyaluronidase at the February 2007 NDPSC Meeting to allow further consultation.

Hyaluronidase

The hyaluronidases are a family of enzymes that degrade hyaluronic acid. By catalysing the hydrolysis of hyaluronic acid, a major constituent of the interstitial barrier, hyaluronidase lowers the viscosity of hyaluronic acid, thereby increasing tissue permeability. It is used in medicine in conjunction with other drugs in order to speed their dispersion and delivery. The most common application is in ophthalmic surgery, in which it is used in combination with local anaesthetics. It also increases the absorption rate of parenteral fluids given by hypodermoclysis, and is an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Methyl salicylate

Methyl salicylate, the methyl ester of salicylic acid, is used as a rubefacient in deep heating liniments, and in small amounts as a flavouring agent. It is also used to provide fragrance to various products and as an odour masking agent for some organophosphate pesticides. Methyl salicylate/methyl salicylate liniment is also known as oil of wintergreen.

The 1983 DPSSC Meeting considered 12 cases of poisonings involving methyl salicylate liquids and creams, noting that 5 mL was likely to be a lethal dose. The Committee agreed to a Schedule 2 entry for human therapeutic use preparations with ≤ 25%, unscheduled for all other preparations ≤ 25% and Schedule 6 when > 25%.

The May 1984 DPSSC Meeting agreed that the intention of the Schedule 2 entry had been to restrict liquid preparations, and that capture of solid compounded forms intended for topical use was unintended. Scheduling consideration was deferred until the August 1984 Meeting where it was agreed that Schedule 5 was appropriate for liquid preparations ≥ 25%, and that CRCs should be used for all preparations ≥ 50% methyl salicylate. The Committee also agreed to delete the Schedule 2 entry. The Schedule 5 and 6 entries at this time were:

Schedule 5

METHYL SALICYLATE in liquid preparations containing 25 per cent or more of methyl salicylate except when included in Schedule 6.

Schedule 6

METHYL SALICYLATE excluding admixtures.

The November 1988 DPSSC noted that some jurisdictions had issue with the above wording and agreed to reconsider the Schedule 5 and 6 entries. The Members foreshadowed the following:

Schedule 5

METHYL SALICYLATE in liquid preparations containing 25 per cent or less of methyl salicylate except in preparations containing less than 5 per cent of methyl salicylate.

Schedule 6

METHYL SALICYLATE **except**:

(a) when included in Schedule 5;

(b) in solid or semi-solid preparations; or

(c) in other preparations containing less than 5 per cent of methyl salicylate.

The Secretariat advised that a search of the Committee records found no indication that this foreshadowed decision was ever subsequently considered.

DISCUSSION

Methyl salicylate

Members recalled the following from the October 2006 NDPSC Meeting regarding methyl salicylate:

- A Member queried the proposed Schedule 5 and 6 methyl salicylate entries. There appeared to be a problem because of the exception for "admixtures" in Schedule 6, noting that a 25% or more preparation in Schedule 5 represents an admixture. The Member proposed removal of the admixtures exception.

- It was highlighted that the minutes of the August 1983 meeting noted that 5 ml was likely to be a lethal dose and it was marketed as 'fragrant oil' at that time. Members also noted that some therapeutic products may contain more than 25% methyl salicylate.
- Members noted that the current entries for methyl salicylate appeared to have inadvertently omitted the inclusion of preparations containing more than 50% methyl salicylate in Schedule 6.
- A Member suggested a solution to the scheduling of methyl salicylate would be to confirm the foreshadowed Schedule 4 entry for internal therapeutic use, and for XXXX to provide advice, including evidence, to support setting a cut-off from Schedule 6 to 5. It was originally proposed that 50% may be a reasonable cut-off, based on the specified CRC cut-off in the SUSDP of the same amount.

Members noted the following from the Micromedex monograph on methyl salicylate.

- Methyl salicylate is a salicylic acid derivative that is irritant to the skin and is used topically in rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It is also used for minor peripheral vascular disorders such as chilblains and as an ingredient in inhalations for the symptomatic relief of upper respiratory-tract disorders.
- Ingestion poses the threat of severe, rapid-onset salicylate poisoning because of its liquid concentrated form and lipid solubility. It is readily absorbed from the gastrointestinal tract and is rapidly hydrolysed to free salicylate. The symptoms, which may appear within 2 hrs, are similar to those of salicylate poisoning, although methyl salicylate is expected to be more toxic because of its lipid solubility. There have been reports of fatalities after ingestion of as little as 4 mL in a child and 6 mL in an adult, although the adult lethal dose is estimated to be 30 mL.
- Methyl salicylate may be absorbed through intact skin. Both the rate and extent of absorption increased after repeated application. A study demonstrated high tissue to plasma ratios following topical application of a methyl salicylate formulation. The results also showed that methyl salicylate is extensively metabolised to salicylic acid in the dermal and subcutaneous tissues after topical application.
- Potentiation of warfarin anticoagulation has been reported after topical application of methyl salicylate preparations.
- Topical Chinese herbal medicinal oils may contain methyl salicylate in variable amounts. Wintergreen oil is also used in aromatherapy.

The Secretariat advised that it had investigated the apparent lack of a cut-off in the current Schedule 6 methyl salicylate. In doing so it noted the foreshadowed decision of 1988 which proposed a scheduling cascade i.e. liquids < 5% exempt, ≤ 25% Schedule 5 and > 25% Schedule 6 with a general exemption for solid or semi-solid preparations. As set out in background above there was no evidence of later consideration of this proposal.

Members considered the following advice from XXXX regarding the scheduling of methyl salicylate, including a cut-off from Schedule 6 to Schedule 5.

- The toxicity of methyl salicylate has been extensively studied in animal bioassays of acute, subchronic, and chronic duration. The following data has been reported:
- Acute oral LD_{50} (rat): 887-1250 mg/kg, consistent with Schedule 6.
- Acute dermal LD_{50}: > 5 g/kg in the rabbit, consistent with Schedule 5.
- Severe eye irritant, consistent with Schedule 6.
- Mild dermal irritation in rabbits at 1%. Moderate to severe irritation in rabbits and guinea pigs > 1%, consistent with Schedule 6.
- Moderately irritating when applied full strength to intact or abraded rabbit skin for 24 hrs under occlusion. However, at 8% it produced no irritation after a 48 hr closed-patch test on human subjects.
- No evidence for genotoxicity was observed in 2 studies with prokaryotic test systems; no data on genotoxicity in mammalian test systems are available.
- In rats, no adverse effects were seen at an oral dose of 50 mg/kg/day in the diet. In dogs, oral doses ≤ 250 mg/kg/day did not result in any adverse effects, however, the liver appeared to be the target organ of toxicity at doses above this level. No toxicity was observed when rats were exposed via inhalation of saturated air (~ 700 mg/m3) after 20 7-hr exposures.
- In hamsters, oral or dermal doses of 1,750 mg/kg/day induced maternal toxicity and increased the incidence of neural tube defects. In rats at up to 6,000 mg/kg/day in petroleum based grease by the dermal route, no developmental effects were observed. However, undiluted methyl salicylate applied to the skin of pregnant rats caused total litter resorptions at 1,000 mg/kg/day (a dose that was reduced from 2,000 mg/kg/day because of excessive maternal toxicity).
- In mice, the NOAEL for reproductive parameters and the other toxic endpoints examined has been reported as 250 mg/kg/day.
- Chronic exposure studies with 2 yr exposure, including extensive pathology, did not indicate any increases in incidences of benign or malignant tumours.
- The XXXX had determined Generally Recognised As Safe (GRAS) levels of methyl salicylate and oil of wintergreen in foods and beverages as indicated in the table below.

Food	Methyl salicylate (ppm)	Oil of Wintergreen (ppm)
Beverages	59	56
Ice cream	27	44
Candy	840	260
Baked goods	54	1,500
Chewing gum	8,400	3,900
Syrups	200	---

- From this it appears that Schedule 6 is appropriate for methyl salicylate, based on oral toxicity and skin and eye irritation. There were no available toxicological data to support a cut-off to Schedule 5. If a cut-off were to be based on extrapolated toxicity then one would need to be confident that eye and skin irritation would be reduced from severe to moderate. On this basis, a 25% cut-off is preferable to a 50% cut-off.

Members were advised that pre-meeting comments were received regarding methyl salicylate.

- XXXX noted that the toxicological review taking into consideration products on the ARTG should also include products utilising oil of wintergreen which is primarily composed of methyl salicylate.
- XXXX noted that the October 2006 NDPSC Meeting agreed to foreshadow consideration of methyl salicylate at the February 2007 NDPSC Meeting to allow a review of toxicological data and scheduling history. The outcome of this review will assist XXXX in providing future assessment of impact of any proposals for scheduling changes.
- XXXX and XXXX noted an interest in this item.

Members agreed that due to oral toxicity and eye/skin irritation, the parent entry for non-therapeutic use of methyl salicylate should be schedule 6 (both liquid and non-liquid). Members discussed whether to set a cut-off to Schedule 5 at 50% or 25%, and agreed that extrapolation of the above toxicology data indicated that 25% was a more appropriate cut-off. Additionally, as ≤ 5% was unlikely to pose any significant risk, the Committee generally agreed that such strengths should be exempt from scheduling. With regards to therapeutic use, the Members agreed that there was risk with internal use at any strength and that all such products should be Schedule 4. Members also agreed that all non-internal therapeutic use should be unscheduled, regardless of strength, as any necessary consumer warnings could be implemented by the appropriate regulator, and there was no need to limit the supply of these products.

Hyaluronidase

Members recalled the following from the October 2006 NDPSC Meeting regarding hyaluronidase.

- The intent to consider the proposed inclusion in Schedule 4 of the animal-derived enzyme "hyaluronidase" to harmonise with New Zealand was inadvertently omitted from the pre-October gazette notice. On this basis, the Committee agreed to consider this matter at the February 2007 NDSPC Meeting.
- Pre-meeting comment which included support for a separate Schedule 4 entry for hyaluronidase. The information in Table 1 considered at the June 2006 NDPSC Meeting incorrectly stated that there were no products listed on the ARTG containing hyaluronidase. There was one injectable product and two medical devices containing hyaluronidase listed on the ARTG. The Committee agreed to foreshadow harmonisation with New Zealand by including hyaluronidase in Schedule 4.

Members noted that no substantive pre-meeting comment was received regarding the foreshadowed consideration of a Schedule 4 parent entry for hyaluronidase. XXXX and XXXX did note an interest.

Members were also advised that the New Zealand classification of hyaluronidase was General Sale, not Prescription as thought at the October 2006 NDPSC Meeting. Members also noted that the one injection product noted at the October 2006 NDPSC Meeting was in fact a medical glue and therefore qualified for an Appendix A general exemption from scheduling. The Committee therefore agreed that there was no need to apply scheduling controls to hyaluronidase, noting that this would also harmonise with New Zealand.

OUTCOME

Hyaluronidase

The Committee confirmed the currently harmonised status of hyaluronidase (unscheduled in Australia, and general sale in New Zealand).

DECISION 2007/49 - 2

Methyl Salicylate

The Committee agreed to:

- capture internal therapeutic use of methyl salicylate in Schedule 4 as this use pattern requires professional management. The Committee further agreed to recommend to New Zealand that it harmonise with this decision;
- exempt remaining therapeutic uses from the requirements of scheduling;

- confirm the CRC requirement for preparations containing ≥ 50% methyl salicylate when in a container ≤ 200 mL; and
- create a Schedule 6 parent entry for all non-therapeutic uses of methyl salicylate due to oral toxicity and skin and eye irritation. These risks are sufficiently reduced at concentrations ≤ 25% to allow a cut-off to Schedule 5. The Committee also agreed that at ≤ 5% there is little risk and that such concentrations do not warrant control by scheduling.

Schedule 4 – New entry

METHYL SALICYLATE in preparations for internal therapeutic use.

Schedule 5 – Amendment

METHYL SALICYLATE – amend entry to read:

METHYL SALICYLATE in preparations containing 25 per cent or less of methyl salicylate **except**:

(a) in preparations for therapeutic use; or

(b) in preparations containing 5 per cent or less of methyl salicylate.

Schedule 6 – Amendment

METHYL SALICYLATE – amend entry to read:

METHYL SALICYLATE **except**:

(a) when included in Schedule 5;

(b) in preparations for therapeutic use; or

(c) in preparations containing 5 per cent or less of methyl salicylate.

1.8.1.2 DEFERRED HARMONISATION PROPOSALS FROM THE JUNE 2006 NDPSC MEETING

1.8.1.2.1 ASPIRIN COMBINED WITH CAFFIENE, PARACETAMOL OR SALICYLAMIDE

PURPOSE

The Committee considered a Trans-Tasman Harmonisation Working Party (TTHWP) recommendation for harmonisation regarding aspirin, paracetamol and salicylamide deferred from the June 2006 NDPSC Meeting.

BACKGROUND

A member indicated to the October 2005 NDPSC meeting that New Zealand was prepared to consider harmonisation with the Australian OTC scheduling and that as most products on the New Zealand market were generally of similar pack sizes, it was unlikely for such products to be affected if New Zealand harmonised with the Australian scheduling of OTC products. It was pointed out however, that the main point of divergence in the scheduling of aspirin products in the two countries was the classification of aspirin combination products. The Committee was also informed that advice would be sought from XXXX with regard to the safety of combination aspirin products if rescheduled to OTC status and in particular, specific comment would be sought on the issue of aspirin and renal disease. The Committee agreed to consider this matter at the February 2006 NDPSC Meeting subject to the availability of XXXX advice.

The February 2006 NDPSC Meeting agreed to defer consideration of the scheduling of aspirin as the advice from XXXX had not yet been received.

The June 2006 TTHWP Meeting noted the completion of the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedules 2, 3, 4 and 8 and equivalent NZ classifications, where available. The TTHWP considered each remaining unharmonised substance and agreed that the TTHWP's recommendations be included on the agenda of the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed the recommendations from the June 2006 TTHWP Meeting and foreshadowed consideration of remaining unharmonised medicines at the October 2006 NDPSC Meeting to allow appropriate public consultation. Similarly, the Committee agreed that the recommendations to NZ to harmonise the scheduling of certain medicines should be referred to the MCC for consideration. The Committee further agreed that consideration of some substances, including aspirin, paracetamol and salicylamide, would need to be deferred to a future meeting to allow a more thorough risk and regulatory impact assessment (Members specifically noted a request from industry to consider harmonisation of aspirin, paracetamol and salicylamide at the February 2007 meeting) and that other substances would remain unharmonised at this time.

The October 2006 TTHWP meeting endorsed the recommendations and actions in relation to each medicine listed in Table 3 "Deferred harmonisation proposals" from the June 2006 NDPSC Meeting, including actions for aspirin, paracetamol and salicylamide. The TTHWP agreed that these actions would be tabled for consideration at the February 2007 NDPSC Meeting to allow appropriate public consultation.

DISCUSSION

XXXX provided a pre-Meeting submission in which XXXX recommended that aspirin in combination with paracetamol, salicylamide or caffeine remain as an S4 item. XXXX main points were:

- XXXX had experienced profound morbidity and mortality in patients associated with compound analgesics, in particular analgesic nephropathy.
- There had been a progressive decline in the incidence of end-stage renal disease (from >15% to 2%) following the banning of OTC sales of compound analgesics in Australia. Patients presenting with analgesic nephropathy are generally between the ages of 60 to 80, instead of 30 to 50 as was seen previously.
- While some reviews suggested that the substitution of paracetamol for phenacetin would limit the nephrotoxicity of compound analgesics, the overall evidence confirms that paracetamol is of particular toxicity, particularly when combined with aspirin and caffeine.
- XXXX noted that when evidence of compound analgesic caused nephrotoxicity became clear, Sweden banned the products in 1969 but Australia did not follow suit until the 1977 NHMRC recommendation.

XXXX provided a pre-Meeting submission in which XXXX recommended that aspirin in combination with paracetamol, salicylamide or caffeine remain as an S4 item. XXXX main points were:

- The nephrotoxicity, gastric toxicity, accelerated ageing process with premature mortality from cardiovascular disease and the increased incidence of urothelial malignancy toxicity of aspirin combinations is well documented and established beyond doubt. The majority view is that it is the combination of aspirin and paracetamol that is toxic to the kidney and that when taken habitually results in analgesic nephropathy. The minimum dose to incur a risk of analgesic nephropathy was never clearly established but was thought to be about 3-5 powders/tablets on most days for about 3-5 years. The constant observation in those detected to have the condition was regular (once or more daily) usage. The dose of the single agents varied but was usually aspirin ~300mg, paracetamol, ~500mg and caffeine citrate about 160mg.
- XXXX believed there was no need for access to aspirin combinations given the toxicity of the combination and the large range of other combination simple analgesics already on the market (MIMS lists 26 combination simple analgesic preparations available at this time). XXXX was unaware of the need for aspirin combinations being expressed by the public or any group in Australia in recent times. They also noted that not a single submission requesting the APC combination products be kept on the market was received by the bodies reporting to and making recommendations to NHMRC in 1979.

- There is no usage of aspirin combinations at the present time as they are not currently marketed in Australia (with the exception of aspirin with a small dose of codeine) but the extent of use of these products before aspirin combinations were placed on S4 in 1979 was substantial. Sales figures from combination analgesics prior to 1979 are not currently available. However, reports indicate that up to 15-20% of all adult females took these preparations with some regularity and some consumers were ingesting up to 20 or more powders a day.
- There was no question that regulatory action taken in the 1970s, first to remove phenacetin from combinations and then to schedule all aspirin combinations as S4 resulted over time in a virtual disappearance of the analgesic syndrome including analgesic nephropathy as a cause of chronic kidney failure. Allowing these combinations to be marketed again in Australia, with its recent record of serious abuse of these same substances, would likely incur the same levels of toxicity in consumers. The risk of this increases markedly if the combination analgesic includes another substance such as caffeine, which is habit forming.
- Any temptation to de-schedule aspirin combinations based on the experience of other countries such as New Zealand should be resisted in view of:
  (a) The lack of published evidence that there was community abuse of combination analgesics in New Zealand.
  (b) The difference in climate that may have contributed to an increased risk of analgesic nephropathy from dehydration accentuating the toxicity of combination analgesics.

XXXX provided a XXXX submission which discussed the scheduling of paracetamol when compounded with caffeine alone and supports the harmonisation of fixed combination paracetamol products with New Zealand. Their main points were:

- In Australia, paracetamol/caffeine combination analgesics are listed as Schedule 4 medicines, as the result of a 1977 NHMRC recommendation that any analgesic combination which includes caffeine should be restricted to Schedule 4 due to the possible association of analgesic nephropathy with the use of these products. However, individual paracetamol containing products, and individual caffeine containing products, are both available exempt from scheduling in open sale. In contrast, a fixed dose combination of paracetamol 500mg and caffeine 65mg has been available exempt from scheduling in New Zealand (in pack sizes of 20 tablets or less) since October 2000.
- This paracetamol/caffeine combination has also been available for General Sale in the United Kingdom and Ireland (both similar to Australia in population type and regulatory status) for 19 and 12 years respectively, and is available over-the-counter in over 50 countries world-wide.
- Paracetamol has been available in Australia since 1956. The efficacy and good tolerability profile of paracetamol have contributed to its popularity. Caffeine is

widely available in caffeinated beverages, soft drinks and food products. There is no maximum limit on the consumption of any of these types of products. The amount of caffeine afforded by two tablets of the paracetamol/caffeine XXXX is comparable to that in a medium strength cup of coffee.

- Caffeine is a stimulant, which by itself is not an analgesic. However, in doses as low as 65 mg, it acts as an analgesic adjuvant (through a variety of potential mechanisms), whereby it augments the analgesic effects of pain relievers such as paracetamol and several large studies, including an analysis of over 30 trials involving more than 10,000 patients, have demonstrated enhanced analgesic efficacy (enhanced analgesia, faster onset of action) when simple analgesics such as paracetamol are administered in combination with caffeine at doses ranging between 65mg to 195mg in a number of different pain states.
- Both paracetamol and caffeine are regarded as being remarkably safe when used at therapeutic doses and there is a low risk of serious expected or serious unexpected adverse events or drug interactions with these products when taken either alone or in combination. With caffeine the most common adverse events are consistent with caffeine's' known pharmacology and include nausea, diuresis, insomnia and CNS stimulation. The severity of adverse events is dose related and an acute, fatal overdose of caffeine is estimated to be 5 – 10g although this is dependant on age, smoking and prior caffeine use. With paracetamol adverse reactions are rare but may include dyspnea and nausea. Several cases of thrombocytopenia have also been reported. A link between paracetamol and analgesic nephropathy has been suggested, but phenacetin has been identified as the major risk factor. Although paracetamol is a metabolite of phenacetin, there is no evidence that paracetamol alone causes analgesic nephropathy and it does not affect renal function at recommended doses. Liver toxicity may result from excessive (over) dosing (12g - 15g in a healthy adult) or where there are other pre-existing factors (eg alcoholism) predisposing to liver damage.
- Debate about the suspected association between kidney disease and use of analgesics has led to concerns about whether caffeine could stimulate an undesirable overuse of phenacetin free combined analgesics. Critical reviews of the published literature have concluded that the available evidence does not support this hypothesis. Dependence behaviour has not been observed with non-phenacetin analgesic preparations containing caffeine or with caffeinated beverages. Despite having a brain-stimulating effect, caffeine does not cause the type of compulsory drug use behaviour as was found with phenacetin-containing powders. Indeed the prominent Australian nephrologist Prescilla Kincaid-Smith reported in the *Medical Journal of Australia* that " … it was after the removal of phenacetin and not caffeine that patients noticed the loss of the mood altering properties of compound analgesics."
- The most common adverse events associated with the combination product are generally not significant and include stomach discomfort, nervousness, dizziness, occasional skin rash and allergic reaction, with insomnia being a possibility due to the

caffeine content. Indeed in New Zealand there has only been one adverse event report (anxiety, tachypnoea, palpitations, increased sweating and emotional lability) in the 5 years the product has been available as a general sale item. Further, in the period of May 2003 to November 2006 there were 48 calls to the Poisons Information Centre relating to the use of the combination product compared to 1353 for XXXX (not all paracetamol) products. Overdosing with this product is not common.

- The worldwide data available from the most recent PSUR showed that between January and December 2005 approximately 26.2 million patients received the combination product with only 11 adverse events being reported, one of which was serious (attempted suicide in a patient who took 8 tablets of the combination, 20 of dimenhydrinate 50mg and 4 of cyclobenzaprine).
- Until the late 1970's triple-active compound analgesics were available open sale in Australia. The main two proprietary brands available at that time were BEX powders and VINCENT'S powders. Both of these brands contained aspirin, caffeine and phenacetin (although the phenacetin was replaced by paracetamol in BEX powders in 1975 and by salicylamide in VINCENT'S powders in 1967). The issue of analgesic nephropathy, associated with the abuse of phenacetin-containing compound analgesics began to emerge in Australia in the late 1960's. During the 1960s and 70s analgesic abuse was common, especially amongst young women, with approximately 60% of the population taking two or more doses of analgesics per day, the highest recorded consumption of phenacetin in the world. During the same period 5 – 15% of autopsies performed in Australian hospitals showed the presence of analgesic nephropathy compared to 0.2% in the UK and US and by 1976 the prevalence of analgesic nephrotoxicity was 20% of the population.
- Triple combination analgesics were implicated as imparting a greater risk of analgesic associated nephropathy than were single or co-formulated analgesics. It must be stressed that every observation described in papers published by Australian nephrologists at this time related to patients with overuse of phenacetin-containing powders not paracetamol or solid dose forms.
- Concerns regarding this led to a worldwide ban on phenacetin in analgesic combinations, implemented in Australia in 1978. In 1979/80 all caffeine containing combination analgesics were rescheduled to Schedule 4 due to the fact that the incidence of analgesic nephropathy did not drop after the banning of phenacetin. It should be noted that Australia was the only country to exert this extra level of control on caffeine containing analgesics.
- Given that end stage renal disease develops over a long period (10-30 years), any reduction in nephropathy as a result of legislation to restrict access to these combination analgesic products would not be expected to have been realised for at least a decade. As such, it has been suggested that this second ban on combination analgesic products in Australia was an overreaction.

- It is clear from the available evidence that analgesic abuse is related to a specific form of interstitial nephritis. However, the exact nature of the causal agent continues to be controversially discussed. Whilst many believed that phenacetin was the key causative component, others favoured the hypothesis that paracetamol (being a major metabolite of phenacetin) when taken in combination with salicylates night have been the main culprit.
- Changes in prescription and self-medication practices over the last 20 years have almost eradicated analgesic nephropathy from the U.K. and Sweden, two countries in which there was previously a high frequency of end stage renal failure due to analgesic nephropathy. A study into the changing patterns of prevalence and age-distribution of analgesic nephropathy in Europe *(Brunner FP, Selwood NH. End-stage renal failure due to analgesic nephropathy, its changing pattern and cardiovascular mortality. EDTA-ERA Registry Committee. Nephrol Dial Transplant 1994; 9(10):1371-1376)* has shown that in Switzerland the rate dropped from 28% in 1981 to 12% in 1990. The authors of the study also noted that there has been an increase from 57 to 63 years in the median age-range for patients with analgesic nephropathy during the same interval. These authors concluded that "some 20 years after withdrawal of phenacetin from the analgesic market, analgesic nephropathy all but disappeared as a cause of ESRF in Sweden and Denmark, and the same may be expected to occur in countries like Switzerland, Belgium, and others in the not too far distant future."
- A further study comparing the evolution of end stage renal disease as a result of analgesic nephropathy *(Michielsen P, de SP. Trends of analgesic nephropathy in two high-endemic regions with different legislation. J Am Soc Nephrol 2001; 12(3):550-556)* in New South Wales, Australia and Flanders, Belgium was conducted. The rationale for choosing these two regions being that both were high-endemic regions for analgesic nephropathy in the late 1970's, but had adopted different legislations to deal with this problem. This difference was that in Belgium whilst phenacetin was banned in the late 1970's there was no further restriction on the sale of combination analgesics, including those containing caffeine.
- The results of the study showed that, despite the ongoing availability of combination analgesics in Belgium, the incidence of analgesic nephropathy has declined steadily at the same rate in NSW and Flanders since the ban on phenacetin. This directly comparative data demonstrates that persisting high consumption of non-phenacetin compound analgesics in Flanders is not associated with a continued problem with analgesic nephropathy. The authors conclude that these data suggest it unlikely that non-phenacetin compound analgesics have a significant role of in the genesis of analgesic nephropathy.
- In 2005 the Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy (SAN) recommended further study into this area. The explicit objective of the study was to examine the nephrotoxicity of newer (phenacetin free) analgesic compounds. The study was designed with an upper age limit for the study population

of 50 years of age in order to avoid contamination by previous phenacetin use. There are no published results available to date. However, the chairman of the International Scientific Advisory Committee for SAN has made a statement available to the relevant Health Authorities. It indicated "that there is no evidence that phenacetin free analgesics or any subgroup including combined analgesics are associated with an increased risk to suffer from nephropathy leading to dialysis."

- The Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy had also recommended that an autopsy study be undertaken to determine whether classic analgesic nephropathy could still be determined at the start of the 21st century. Consecutive autopsies of 616 adults performed at the Basle Institute of Pathology between November 2000 and February 2002 were analysed for papillary necrosis, urothelial capillary sclerosis and analgesic nephropathy. Not a single case of papillary necrosis or analgesic nephropathy could be detected preceding histological analysis. Histologically, the most frequent lesions were vascular in 57.8% of kidneys followed by glomerular lesions in 13.1% (mostly diabetic glomerulosclerosis). Tubulo-interstitial lesions, mostly pyelonephritis were detected in 9.3% with only a single case of classic analgesic nephropathy with bilateral complete papillary necrosis and ureteral capillary sclerosis detected. In another five cases, complete papillary necrosis was detected associated with pyelonephritis, hydronephrosis or in completely shrunken kidneys. However, in the absence of capillary sclerosis, a histopathological diagnosis of classic analgesic nephropathy could not be made in any of these five cases. The authors of the study concluded that "the classic analgesic nephropathy has disappeared some 20 years after the removal of phenacetin from the analgesic market despite the fact that mixed analgesics containing paracetamol, the main metabolite of phenacetin, have continued to be popular and widely used drugs."
- Australian data showed a reduction from approximately 32% of all end-stage renal disease in the late 1970's to under 10% in the late 1990's. This was comparable with data from other countries — for example, Brunner et al reported a reduction in prevalence of analgesic nephropathy in Switzerland from 28% in 1981 to 12% in 1990 despite the continuing popularity of combination analgesics.
- Data from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry was used to identify trends in the number of people with end stage renal disease from analgesic nephropathy have been evaluated to establish whether there has been a change in the disease patterns in more recent years, particularly beyond 1998. This analysis has demonstrated that there is a continuing downward trend in the prevalence of analgesic nephropathy, with current figures for Australia being less than 5% of all end-stage renal disease. The downward trend is also evident in New Zealand, where combination analgesics are available (although the trend appears to be less apparent because the prevalence was extremely low at the outset).
- Analysis of the data by age group supports the conclusion that the prevalence of analgesic nephropathy has declined since the ban on phenacetin. Data for 2005

showed that the incidence of analgesic nephropathy as a cause of new patients with end stage renal disease to be 26 per million population in the 75-84 year age group, corresponding data for other age groups are 24 (65-75 years), 4 (55-64 years) and 0 (45-54 years),

XXXX then discussed the public health considerations of allowing a paracetamol and caffeine only combination into the Australian setting as a non-prescription medication. In support of this rescheduling of paracetamol and caffeine combinations XXXX made the following points:

- Allowing a paracetamol/ caffeine combination to be supplied as a non prescription medication would meet an as yet unmet need in the community by giving those patients who are unable to use NSAID-based analgesics due to contraindications or precautions an alternative treatment option.
- The amount of caffeine provided by a two tablet dose of the paracetamol/ caffeine combination would be XXXX, roughly the same amount as in a medium strength cup of coffee and less than many currently available caffeine stimulant and weight loss products. Further, many speciality coffees sold from coffee shops may have up to 564mg/ 16oz cup, as much as would be obtained by taking eight tablets (the maximum daily dose) of the paracetamol/ caffeine combination. The maximum proposed pack size for the paracetamol/ caffeine combination XXXX as opposed to 70 tablets (7000mg caffeine) for XXXX.
- Currently no paracetamol/caffeine combination analgesics are available in Australia making it impossible to show current use patterns. However, volumetric sales data from New Zealand indicate that the paracetamol/ caffeine combination product is consumed far less than is paracetamol alone despite its availability in general sales outlets, with sales of the combination making up approximately XXXX
- XXXX had conducted further studies regarding extent and patterns of use of the paracetamol/ caffeine combination in New Zealand using consumer data collected in 2002. This data showed that over a 24 week period XXXX. These figures had dropped slightly when the same analysis was conducted in 2003.
- XXXX noted that paracetamol and caffeine, whether alone or in combination have a low potential for harm from inappropriate use. Most cases of paracetamol overdose are intentional. It is suggested that the maximum pack sizes for General Sale XXXX contain 20 tablets or less with the Pharmacy Medicine packs being larger. If purchase patterns reflect those for the combination in New Zealand, it would be expected that the majority of consumers will purchase the 16 tablet pack. As such, the potential for risk of overdose with the paracetamol/ caffeine combination would be no different from that with other currently available unscheduled paracetamol only preparations. The lethal dose of caffeine in adults appears to be 5-10 g, which is the equivalent of between XXXX tablets, thereby offering a high margin of safety when compared to the commonly purchased New Zealand general sale pack of 16 tablets.

- For the combination product early symptoms will be elicited due to its caffeine content. Assuming a minimum toxic dose of 15 g (30 tablets) of paracetamol, a concurrent ingestion of 1.95 g caffeine will occur. This will produce significant non life-threatening symptoms such as gastrointestinal disturbance, tremors, agitation and tachycardia, and is likely to lead to early detection of overdose, and potentially timely antidote treatment for paracetamol poisoning. The presence of caffeine could be considered to help mitigate risk of overdose with XXXX.
- XXXX also stated that the paracetamol/ caffeine combination has an extremely low potential for abuse, despite some concern regarding the mild CNS stimulant profile of caffeine and whether it could promote analgesic dependence. Critical reviews of the published literature have concluded that the available evidence does not support a pivotal role of caffeine in initiating or sustaining overuse of analgesics. Further to this a XXXX review conducted by an expert in the field of drug dependence concluded that caffeine's pharmacology and patterns of use differ to that of prototypic dependence-producing substances, caffeine is a relatively weak biological reinforcer and is readily distinguished from dependence producing stimulants and therefore that potential risk from caffeine causing dependence or inappropriate use in combination with analgesics appears minimal.
- XXXX also noted that both paracetamol and caffeine have wide therapeutic indexes, with large margins between their recommended daily dose and that being regarded as required for overdose and lethality.
- Fixed dose caffeine-paracetamol combination analgesics have been available over-the-counter in many markets around the world for several years with no substantial documented adverse effects or dependence. There is no compelling reason, based on concerns of safety or otherwise, to continue to restrict the availability of this medication to a prescription only status in the Australian marketplace.
- Based on the evidence presented in this document, the NDPSC should recommend that Australia harmonise with the scheduling currently in place in New Zealand for this same combination.

XXXX also provided a further XXXX submission from an "Expert Panel Meeting" which was convened to discuss the safety and utility of paracetamol/ caffeine combinations in the non-prescription environment. Their main points were:

- The Panel considered the current scheduling of paracetamol/ caffeine combination analgesics. The Panel's recollection of events leading up to the re-scheduling of caffeine-containing analgesics was that it was largely prompted by the pivotal work of Priscilla Kincaid Smith, who recognised the condition of analgesic-associated nephropathy amongst Australian analgesic abusers. One panel member recalled his experience as a nephrologist in NSW in the 1970s where about one third of renal transplants were preformed in patients with analgesic nephropathy.

- Some members of the group commented that the perception at that time was that the caffeine component of the combination analgesics caused the preponderance of use (i.e. it made it "moreish"). Despite the almost ubiquitous availability of caffeine today the group felt that there may be still be a perception that caffeine may have dangers associated with it.
- The Panel discussed the issues and processes of Trans-Tasman harmonisation. They surmised that were it to go ahead, harmonisation of paracetamol/caffeine combination analgesics would most likely be to the lowest common denominator — that being to make such combination exempt from scheduling in pack sizes of 20 tablets or less and Schedule 2 (Pharmacy Only) for larger pack sizes.
- The Panel considered the historical concerns regarding analgesic nephropathy, in particular why the incidence was higher in Australia. The Panel considered that the higher consumption of phenacetin and the Australian climate (which may cause dehydration) when combined with the heavy promotion and little control over the purchase and consumption of "powders" were the likely drivers for this.
- The Panel also discussed the implications of the lag time between stopping the analgesics and then seeing a reduction in renal problems. A member explained that when a person stops taking/abusing analgesics the renal problems do not progress, rather their GFR will be at a lower base-point which may make them more likely to have renal problems in the future. The Panel agreed that the comparative data from Flanders and NSW showed that keeping combination analgesics in the market place had not resulted in a continuance of renal problems and that it would be unlikely that such problems would begin to emerge in the future. The Panel also agreed that the data showed that it was phenacetin which caused the problems, not the use of combination analgesics *per se*.
- The Panel considered the efficacy of paracetamol/ caffeine combination analgesics and noted that the studies presented to it were of high quality and support an adjuvant effect of caffeine in combination with paracetamol and that the effect size was approximately 1.5 i.e., the addition of caffeine to paracetamol produced half as much analgesic effect again as does paracetamol alone. Therefore the Panel felt that were paracetamol-caffeine combinations to be made available they could have an overall public health benefit by providing an alternative to codeine combination products and/or NSAIDs, both of which have well documented safety issues.
- The Panel also specifically considered the safety of paracetamol/ caffeine combination analgesics. The Panel felt that there was sufficient data to demonstrate that the degree of analgesic-associated nephropathy previously reported with phenacetin combination analgesics was not apparent with paracetamol/caffeine combinations. The Panel also felt that there was no evidence of an additional nephrotoxic effect when caffeine was added to non-phenacetin containing analgesics and that nephrotoxicity was specifically related to the overuse of phenacetin containing products.

- The Panel agreed that dependence behaviour has not been observed with non-phenacetin analgesic preparations containing caffeine nor with caffeinated beverage and that the inclusion of caffeine in phenacetin containing compounds had not contributed to the abuse of these substances.
- The Panel also agreed that the addition of the caffeine may provide some benefit in terms of overdose. The opinion of the group was that if a person took an entire packet (24 tablets of paracetamol 500 mg plus caffeine 65 mg) then they would be expected to vomit due to the caffeine dose (1560 mg), however if the number of tablets taken was not significantly high to produce caffeine overdose then this benefit would not be apparent.
- Overall the Panel felt that the available evidence demonstrated that paracetamol-caffeine combinations are effective and confirm the analgesic adjuvant effect of caffeine across a number of different pain states and supports the view that the availability of paracetamol-caffeine combinations would not lead to an increase in analgesic associated nephropathy. Based on the above, there is no compelling reason why this group would not support the harmonisation of paracetamol-caffeine combinations between Australian and New Zealand.

XXXX provided a submission in which XXXX endorsed the position of XXXX not to support the rescheduling proposal for the following reasons:

1. The risk of re-exposing the Australian community to compound analgesic preparations that were originally banned due to their severe nephrotoxicity; and
2. A lack of evidence of superiority over available analgesics.

- XXXX also voiced concern regarding the combination of aspirin and caffeine which, while caffeine has the effect of enhancing aspirin analgesia, may encourage people to take more of a potentially toxic medication.
- XXXX believed that the New Zealand experience of analgesic nephropathy differs significantly from the Australian and should not be used as a comparator. XXXX also stated that due to this, the trans-Tasman harmonisation principle of adopting the least restrictive scheduling (i.e., the NZ scheduling) should not occur in this instance in the interests of public health and safety.

XXXX provided a submission in which XXXX supported the harmonisation of the aspirin combination schedule entry with New Zealand. Their main points were:

- In New Zealand, medicines are classified according to their active ingredients. If the medicine has more than one active ingredient, the active with the most restrictive classification determines the classification of the product. However, in Australia products containing two or more of aspirin, paracetamol, caffeine or salicylamide are Schedule 4 medicines and have specific schedule entries reflecting this status.

- The Schedule 4 entries for aspirin, paracetamol and salicylamide were a result of the 1977 NH&MRC recommendation that any analgesic combination including caffeine should be included in Schedule 4 due to the association of analgesic nephropathy with the use of these products. It is important to recognise that this review was conducted over 30 years ago, and is unlikely to be as relevant today. During that time, caffeine-containing analgesics have been available globally without there being an increased association with nephropathy resulting in significant regulatory action. Maintenance of such a restriction via a scheduling in Australia is not appropriate, but rather, should be aligned with the approach taken in New Zealand.
- XXXX stated that the appropriate method for determining the safety of a specific combination of substances is via the registration process conducted by the TGA, not the scheduling of the substance by the NDPSC. Any significant safety concerns would be reflected in the fact that such combinations would not be approved.
- Thus, it would be appropriate to amend the Australian scheduling status of aspirin to remove the Schedule 4 entry for combinations containing caffeine, salicylamide and paracetamol. This would help achieve harmonisation of aspirin scheduling with New Zealand, and also reflect an appropriate regulatory approach to scheduling whereby the active with the most restrictive classification determines the classification of a combination product, with safety being evaluated and determined during product registration
- XXXX noted that there are currently only 3 aspirin/ paracetamol and/ or caffeine products on the ARTG and they are all export only listed, i.e. none of these combinations are currently registered/ listed for use in Australia. Therefore any new combination products would be required to undergo evaluation for safety and efficacy by the TGA before they could be supplied to the Australian market.
- XXXX provided an amended wording for the aspirin schedule entries, noting that while they do no achieve complete harmonisation with New Zealand it will have the effect of harmonising products in the marketplace:

  <u>Schedule 2</u>

  ASPIRIN **except**:

  (a) when included in Schedule 4, 5 or 6;

  (b) in individually wrapped powders or sachets of granules each containing 650 mg or less or aspirin when:

  (i) enclosed in a primary pack that contains 12 or less powders or sachets of granules; and

(ii) compliant with the requirements of the *Required Advisory Statements for Medicine Labels;*

(c) in tablets or capsules when:

(i) packed in a blister or strip packaging or in a container with a child-resistant closure;

(ii) in a primary pack that contains 25 or less tablets or capsules, each containing 325 mg or less of aspirin, or in a primary pack of not more that 16 tablets or capsules, each containing 500 mg or less of aspirin; and

(iii) compliant with the requirements of the *Required Advisory Statements for Medicine Labels;*

(d) in tablets or capsules when:

(i) packed in a blister or strip packaging or in a container with a child-resistant closure;

(ii) in a primary pack that contains 100 or less tablets or capsules, each containing 100 mg or less of aspirin, when packed and labelled for the prevention of cardiovascular disease or for the inhibition of platelet aggregation; and

(iii) compliant with the requirements of the *Required Advisory Statements for Medicine Labels;*

Schedule 4

ASPIRIN for injection

A Member noted that there was reasonably compelling evidence, albeit circumstantial, for allowing the combination of paracetamol with caffeine to be down scheduled as this combination does not appear to be significantly nephrotoxic in the way that phenacetin and caffeine or phenacetin, caffeine and aspirin in combination were. The member also noted that New Zealand had never had the problems with abuse of these substances in the way that Australia did. The Member stated that there was good epidemiological evidence from countries which did not ban combination analgesics, but simply removed phenacetin, that their levels of analgesic nephrotoxicity were at the same levels as Australia's who had effectively banned them whether they contained phenacetin or not. The Member noted that there were no head to head studies of phenacetin and paracetamol and therefore assessment of the risk of paracetamol combinations would have to be based

on epidemiological studies and animal models. The Member also noted that animal models did show that enough paracetamol will cause nephrotoxicity, but that it is usually a crystal nephropathy, not analgesic nephropathy. The Member felt that there was enough information provided to reinforce the current scheduling of aspirin, paracetamol and caffeine combinations and that it should be recommended to New Zealand that they adopt this scheduling. The Member also felt that for paracetamol and caffeine that there was evidence to suggest that the combination may not be as nephrotoxic as phenacetin and that rescheduling is probably unlikely to make any impact on the incidence of renal nephropathy. The Member also noted however that, as per XXXX submission, that the two countries have different issues to consider such as climate and likelihood of dehydration and therefore there are grounds for them having differing scheduling for these substances even though the data from New Zealand shows no evidence of overuse, misuse or high levels of AEs.

Members discussed the exact wording of the gazette notice and agreed that the wording did not capture analgesics which contained only paracetamol and caffeine. Thus, the Committee agreed that consideration of paracetamol with caffeine should be gazetted for the June 2007 Meeting. Members felt that this would by no means set a precedent (given that XXXX submission was effectively a rescheduling application for paracetamol and caffeine) because this was an ongoing harmonisation issue which needed to be resolved as soon as possible.

It was agreed that the Committee should once again seek advice from XXXX on the dangers of nephrotoxicity with paracetamol and caffeine only combinations.

In regards to combination analgesics containing aspirin, there was consensus that the scheduling of such products should remain unchanged. Overwhelmingly, specialist colleges with expertise in the area strongly recommended against change and gave sound public health reasons as to why such products should remain in Schedule 4. Further to this, there was little or no evidence presented as to how such combination products are superior over any analgesics already available OTC in Australia. Indeed, the New Zealand Member asked that the Committee recommend to New Zealand that they reconsider the scheduling of combination analgesics containing aspirin with caffeine, paracetamol, phenacetin or salicylamide and that they consider harmonising with Australia.

OUTCOME

The Committee agreed:

- that due to the risk of nephrotoxicity, the current scheduling of aspirin when in combination with paracetamol, caffeine or salicylamide remained appropriate.
- to foreshadow the consideration of paracetamol when in combination only with caffeine for the June 2007 NDPSC Meeting.

1.8.1.2.2 IRON COMPOUNDS, SELENIUM, VITAMIN A

PURPOSE

The Committee considered a Trans-Tasman Harmonisation Working Party (TTHWP) recommendation for harmonisation regarding iron compounds, selenium and vitamin A deferred from the June 2006 NDPSC Meeting.

BACKGROUND

Selenium

Within the SUSDP, the cut-off to exempt selenium for external use is currently harmonised at 3.5% selenium sulfide (outcome of the June 2003 NDPSC meeting), which is equivalent to 2.48 % selenium, but the cut-off to exempt selenium for internal use has remained unharmonised. In addition, NZ has no classification for selenium for internal use under Prescription Medicine but Australia has an S4 entry for over 100 mcg per daily dose.

The June 2004 TTHWP Meeting agreed to recommend the exemption from scheduling of preparations of selenium for internal use containing 150 mcg or less selenium per daily dose, amend the Schedule 2 entry to include internal use preparations containing 150-300 mcg/day selenium and to amend the Schedule 4 entry to include internal use preparations containing more than 300 mcg/day selenium. The 300mcg/ day value is based on epidemiological studies by Yang *et al* which established that 300mcg/ day is the safe upper level for selenium supplements. The Secretariat confirmed that this recommendation was never referred to the full NDPSC.

The toxicity of selenium depends on the nature of the selenium compound, particularly its solubility. Thus, selenium sulphide is much less toxic than selenite, selenate and selenomethionine. Selenium toxicity is cumulative. Chronic selenium poisoning, or selenosis, is associated with changes to the hair, nails, skin lesions and clinical neurological effects such as peripheral hypoaesthesia, acroparasthaesiae, pain and hypereflexia; numbness, convulsions and paralysis may then develop. Studies undertaken in subjects living in seleniferous areas of the USA and China indicate that selenosis is associated with intakes greater than 910 mcg/day (0.015 mg/kg for a 60 kg adult).

Supplementation trials in human volunteers with 200 mcg/day for 10 years did not result in selenosis (Clark *et al*., 1992). Other data from supplementation trials indicate that doses of up to 388 mcg/day selenium/day for shorter periods are without apparent ill effects, although a formal clinical examination for symptoms and/or signs of selenosis was not always made.

Vitamin A

The current scheduling of vitamin A in the SUSDP exempts topical preparations containing 1% or less of vitamin A and preparations for internal use containing 100 IU (equal to 30 micrograms of retinol equivalents – *Retinol equivalents (RE) are the most commonly used unit to measure amounts of Vitamin A. 1 IU is equal to 0.3mg RE. Please note that the Committee discussed the issue of REs in more detail later*) or less of vitamin A. Topical preparations XXXX of Vitamin A were recommended for exemption from Scheduling at the November 1991 DPSSC Meeting on the basis that they did not constitute a risk of teratogenicity. At the November 1995 Meeting the wording for the Schedule 4 vitamin A entry was altered to exempt only topical preparations containing 1% or less of vitamin A. At the same Meeting the Committee agreed that exemption from vitamin A warning statements was appropriate for preparations containing less than 100 IU per dosage unit or 100 IU per gram on the basis that a supplement of 5000 IU coupled with a dietary intake of 6000 IU was accepted as safe. At that meeting, the Committee noted that setting the cut-off level at 100 IU per dosage unit for divided preparations and 100 IU per gram for undivided preparations i.e. 50 dosage units or 50 g respectively would be needed to reach the 5000 IU cut-off level referred in Schedule 4.

In addition, products for internal use containing 5000 IU (equal to 1500 micrograms of retinol equivalents) or less of vitamin A may also be exempted under the current scheduling provisions provided they are labelled with statements including those which specify the adult recommended daily intake of 2500 IU vitamin A from all sources, and warnings relating to use during pregnancy. Products exempt under this reverse scheduling should be labelled with a warning that taking in excess of 8000 IU of vitamin A can cause birth defects and that if a woman is considering becoming pregnant or is pregnant, vitamin A supplements should only be taken after consultation with a doctor or pharmacist.

NZ currently classifies vitamin A preparations containing more than 3000 micrograms of retinol equivalent (10,000 IU Retinol) per recommended daily dose as 'Prescription Medicine'. Parenteral preparations are available as 'General Sale' medicines. The NZ cut-off of 3000 micrograms of retinol equivalents appears to have been derived from the NHMRC Upper Level of Intake for adults which is stated as 3000 micrograms of retinol equivalents.

The June 2004 TTHWP Meeting recommended that the that the issue of bone fracture associated with vitamin-A intake (supplementation + dietary) be the subject of a further literature review and that the outcome be referred to the October 2004 meeting of the NDPSC for consideration. However this was not considered at the Meeting or at further Meetings.

Iron Compounds

The November 1995 NDPSC Meeting considered a submission from the Compliance Branch of TGA requesting clarification in the SUSDP that it was not the intention of the Committee to include colouring agents in the schedule entries, in particular iron oxide. The submission had been considered by the Committee out-of-session and in-principle agreement given to exempting from Schedule 2 preparations containing 4.2 mg or less of iron oxide. The matter before the Committee was to consider whether a cut-off at greater then 4.2 mg should be established and whether there was a need to amend the SUSDP to clarify the intent of the Committee. The Committee was advised that products were currently available containing more than 5 mg of iron oxide per dosage unit and that a cut-off level of 10 mg per dosage unit would be appropriate for known products. On the basis of this information, the Committee considered that a cut-off level of 10 mg of iron oxide was appropriate and agreed to amend the Schedule 2 entry for iron to exempt 10 mg of iron oxide per dosage unit when present as an excipient in the casing or coating of divided preparations.

The May 2001 NDPSC Meeting reconsidered the Schedule 2 entry for iron, on the request of the NZ MCC to harmonise with the NZ daily dose limit of 24 mg or less elemental iron for 'general sale', with no restrictions on pack size. The Committee agreed to harmonise the cut-off to exempt at 24 mg or less of iron in S2, but applied a 600 mg total elemental iron restriction to the pack size, to minimise the risk of poisoning in children.

The August 2001 NDPSC Meeting considered post-meeting comments relating to the May 2001 decision on iron compounds from XXXX. The submissions opposed the pack size restriction in S2 and proposed that the pack size restriction be removed for exempt preparations. The Committee agreed to vary the May 2001 decision and removed the pack size limit restriction on products labelled with a recommended daily dose of 5 mg or less of iron, but retained the pack size restriction of 600 mg for products labelled with a daily dose of > 5 mg but < 24 mg or elemental iron.

The November 2001 NDPSC Meeting agreed to further revise the S2 entry for iron in the SUSDP, to reinstate the exemption for products labelled with a recommended daily dose of 24 mg of iron. In addition, the Committee also agreed to correct an anomaly in the entry and specified a maximum recommended daily dose limit of 24 mg for divided dose preparations containing ≤ 5 mg of iron. It was also proposed at the November 2001 meeting that the pack size limit be increased to 750 mg for products containing > 5 mg iron, when labelled with a recommended daily dose of 24 mg or less of iron. This proposal was based on the rationale that this pack size limit would allow 30 days supply of iron products containing 21-24 mg in a single pack.

The February 2002 NDPSC Meeting amended the Schedule 2 entry for iron compounds to raise the pack size limit from 600 mg to 750 mg. The October 2002 NDPSC Meeting then considered a request for clarification relating to the Schedule 2 entry for iron

compounds, specifically in relation to iron oxides when present as an excipient. The Committee confirmed that the cut-off for exemption for iron oxides in Schedule 2 of the SUSDP applied to preparations containing less than 10 mg of total iron oxides or 1% of total iron oxides (not the equivalent iron content). However, the Committee was of the view that the existing Schedule 2 entry for iron compounds did not clearly reflect this intent and agreed that the matter be referred back to the February 2003 Meeting to amend the entry for consistency with the intent of the Committee.

The February 2003 NDPSC Meeting agreed to amend the Schedule 2 entry for iron compounds to exempt 10 mg or less in divided preparations and 1% or less in undivided preparations of total iron oxides when present as an excipient. However the pack size was inadvertently change from 750 mg or less to 600 mg or less. The Committee considered post meeting comment regarding this at the June 2003 Meeting and agreed to restore the pack size to 750 mg through an editorial amendment to the original decision arising from the February NDPSC Meeting, with the effective date remaining 1 September 2003.

Previous TTHWP Considerations:

The June 2006 TTHWP Meeting noted the completion of the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedules 2, 3, 4 and 8 and equivalent NZ classifications, where available. The TTHWP considered each remaining unharmonised substance and agreed that the TTHWP's recommendations be included on the agenda of the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed the recommendations from the June 2006 TTHWP Meeting and foreshadowed consideration of remaining unharmonised medicines at the October 2006 NDPSC Meeting to allow appropriate public consultation. Similarly, the Committee agreed that the recommendations to NZ to harmonise the scheduling of certain medicines should be referred to the MCC for consideration. The Committee further agreed that consideration of some substances, including iron compounds, selenium and vitamin A, would need to be deferred to a future meeting to allow a more thorough risk and regulatory impact assessment and that other substances would remain unharmonised at this time.

The October 2006 TTHWP meeting endorsed the recommendations and actions in relation to each medicine listed in Table 3 "Deferred harmonisation proposals" from the June 2006 NDPSC Meeting, including actions for Vitamin A, selenium and iron. The TTHWP agreed that these actions would be tabled for consideration at the February 2007 NDPSC Meeting to allow appropriate public consultation.

DISCUSSION

A pre-Meeting submission was received from XXXX who provided information regarding the current recommended daily intakes of these substances. They made recommendations for updating the scheduling of them. Their main points were:

- The units for expressing Vitamin A activity should be updated to the commonly used retinol equivalents (RE) instead of the international units (IU) currently used in the entries. The Committee noted that NZ currently lists in Retinol Equivalents.
- The values in the SUSDP and New Zealand classification should be based on Australian/New Zealand RDIs (700 REs for both men and women) instead of the 5000IU value which is probably based on earlier US criteria.
- It is appropriate to have a restriction on the amount of Vitamin A that is available per dosage given the potential for retinol/retinoic acid to be a teratogen.
- Clarification is needed as to whether beta-carotene supplements are included or excluded from the Schedule 4 entry for Vitamin A, given that beta-carotene supplements are readily available in pharmacy outlets.
- The cut-off values for iron in the SUSDP are higher than the RDI for most groups of patients. These levels should be based on the Australian/ New Zealand RDIs, even though excessive iron intake is likely to result in gastrointestinal symptoms and thus be self limiting. Also, as the current RDI for iron is above current Upper Limit (UL) for very young children and the prevalence of voluntary dosing of children by parents without medical supervision is unknown, it may be appropriate to limit the dosage of iron in over-the-counter preparations.
- Restrictions to the amount of selenium per dosage unit seems appropriate given that excessive selenium can be difficult to detect and also given the adverse events which it can cause in large amounts. Further, as the UL for very young children is close to the RDI for selenium, some consideration should be given to age-related dosages in the SUSDP entries.
- The values for selenium in the SUSDP should be based on the Australian/ New Zealand RDIs, i.e. 50-70 micrograms/ day.

A pre-Meeting submission was received from XXXX who provided information regarding the current recommended daily intakes of these substances. Their main points were:

- The current Nutrient reference values, including recommended daily intakes, were developed jointly with the New Zealand Ministry of Health.
- They also provided the publication *Nutrient Reference Values for Australia and New Zealand* which details the current RDIs for Vitamin A, Iron and Selenium and the rationale for setting each of these values.
- The nutrient reference value for vitamin A should be expressed in terms of retinol equivalents (RE). One RE is defined as the biological activity associated with 1 μg of all-*trans* retinol. Although there is some ongoing discussion in the literature about the conversion rates for carotenes, 6 μg all-*trans* β-carotene and 12 μg of α-carotene, β-cryptoxanthin and other provitamin A carotenoids have been retained as the conversion figures as being equivalent to 1 RE. 1 IU of retinol is equivalent to 0.3μg

REs. These traditional conversion rates align more with the sources of carotenes in the Australian and New Zealand diets. They are also in line with the most recent decision of the FAO, (FAO:WHO 2001) who concluded that the literature to date was insufficient to justify a change in conversion rates. The critical adverse event for determining the upper level of intake of vitamin A was teratogenicity in women of child-bearing age, and for other adults liver abnormalities.

- Beta-carotene has no upper level of intake as the metabolic conversion of beta-carotene to vitamin A is regulated by vitamin A status and excess intake has not been associated with vitamin A toxicity.
- Deficiency in vitamin A can result in abnormal dark adaptation, followed by xerophthalmia but is uncommon in Australia and New Zealand. The New Zealand Children's Survey, 2002 (MOH 2003) did, however, state that a significant proportion of Pacific children and Maori males might be at risk of inadequate intakes.
- The method used to set Estimated Average Requirements (EARs) in this document was based on an estimate of the amount of dietary vitamin A required to maintain a given body-pool size in well-nourished subjects (Olson 1987, FNB:IOM 2001).
- Selenium functions as an antioxidant and in redox reactions and thyroid metabolism. It exerts its effects as a constituent of several selenoproteins, the most important of which are glutathione peroxidases (GP_xs), selenoprotein P, iodothyronine 5'-deiodinases and thioredoxin reductases (TrxRs). In Australia and New Zealand, the main dietary sources are seafood, poultry and eggs and, to a lesser extent, other muscle meats. The absorption of selenium from food is about 55-70%. Low soil selenium levels in New Zealand mean that dietary intakes and selenium status are lower than in many other countries.
- Excess selenium intake is excreted in urine, with the kidneys accounting for 50-60% total excretion. The rest is excreted via faeces, skin, hair and, at high intakes, expired air. Selenium deficiency results in a condition called Keshan Disease, an endemic cardiomyopathy occurring in low selenium areas of China that is responsive to sodium selenite supplementation. Keshan Disease may occur at intakes of selenium of 20 μg/day or less, however, some features of the disease cannot be explained solely on the basis of low selenium status, so Keshan Disease is thought to depend on the presence of additional factors such as a virus, mineral imbalance or environmental toxins. Other conditions such as Kashin-Beck Disease may also be caused by selenium deficiency.
- Indicators that have been used for assessing nutrient reference values include the existence of Keshan Disease, selenium in hair, nails and blood or GP_x and selenoproteins in blood. Whilst some countries base their minimum requirements on levels at which no Keshan Disease is evident in susceptible populations, most use measures of GP_x and other blood measures in response to varying intakes of selenium.

- In Australia and New Zealand the main sources of iron intake are wholegrain cereals, meats, fish and poultry. To achieve iron balance, adult men need to absorb about 1 mg/day and adult menstruating women about 1.5 mg/day, although this is highly variable. Towards the end of pregnancy, the absorption of 4-5 mg/day is necessary and requirements are higher during periods of rapid growth in early childhood and adolescence. Inadequate iron intake can lead to varying degrees of deficiency, from low iron stores, to early iron deficiency and iron-deficiency anaemia. These biochemical measures, rather than the functional indicators of iron deficiency (eg, impaired cognitive and immune function, reduced physical work capacity) which can be difficult to relate directly to a specific dietary intake, are used as the key indicators in setting the iron requirements.
- It is difficult to achieve a steady state with iron because it is highly conserved in the body. For these reasons, factorial modelling rather than the classical balance study method is used to determine the average requirements for the various age, gender and physiological states. This factorial modelling proposes daily physiological requirement for absorbed iron based on estimates of basal losses and, where relevant, menstrual losses and needs for iron accretion in periods of growth such as childhood, adolescence or pregnancy. These accretion needs are estimated from known changes in blood volume, foetal and placental iron concentration and increases in total body erythrocyte mass. The estimated average requirements (EARs) are based on the need to maintain a normal, functional iron concentration, but only a small store (serum ferritin concentration of 15 μg/L)

There has been one media reports of fatal a overdose with selenium. This case report is of a 75 yr old male who suffered a myocardial infarction and died six hours after ingesting 10 grams of selenium (10,000 times the daily dose) as an alternative prostate cancer treatment. ADRAC to date have had no reports of adverse reactions related to overdose with selenium.

XXXX provided a pre-Meeting submission in which XXXX:

- Requested that, with regards to iron compounds, that the exclusions with regard to excipients be maintained in context to any Trans-Tasman harmonised schedule.
- XXXX supported the retention of the exemption permitting unscheduled preparations of 3.5% selenium sulphide and recommended that consideration be given to increasing the daily dose of selenium to 150μg per day which is in line with New Zealand scheduling. XXXX noted that the difference in scheduling between the two countries is due to low selenium intakes in New Zealand.
- XXXX recommended that the differences between unit expressions of IU and μg be reconciled as part of the considerations for Vitamin A.

XXXX made submissions reserving the right to comment further on any scheduling changes made by the Committee.

A Member stated that a key in the consideration of the scheduling of these substances is that the Committee now has access to a joint Australia/ New Zealand document (*Nutrient Reference Values for Australia and New Zealand)* provided by the NHMRC and the Health Research Council in New Zealand which contains a large body of evidence based information examining the safety and toxicity of these substances. The Member noted that the document provides the maximum daily doses for all substances and that the difference in the scheduling for iron comes down to pack size, for selenium the document recommends changing the maximum amount of selenium per day permitted in an unscheduled product than New Zealand currently schedules and suggests that the counties compromise on the scheduling of Vitamin A and pick up Retinol Equivalents as the unit of measurement. The Committee felt that it was appropriate to use the expertise of this document to help it make its scheduling decisions for these substances and that the two countries should be aligning and harmonising their scheduling in line with the document.

OUTCOME

Iron Compounds

The Committee agreed that the current scheduling of iron compounds was appropriate and:

- to recommend to New Zealand that they harmonise with Australia on pack size for total elemental iron in order to minimise the risk of poisoning in children;
- as New Zealand does not schedule iron oxide, the scheduling for iron salts should be considered as essentially harmonised.

DECISION 2007/49– 3

Selenium

The Committee agreed:

- as per decision 11/2 of the TTHWP, to adopt a cut-off to exempt preparations for internal use containing 150 mcg or less selenium per daily dose; amend the Schedule 2 entry to include internal use preparations containing 150-300 mcg/day selenium; amend the Schedule 4 entry to include internal use preparations containing more than 300 mcg/day selenium;
- as selenium sulfide is the least toxic of the selenium salts and 3.5% selenium sulfide is equivalent to 2.5% elemental selenium, recommend to New Zealand that they adopt the Australian scheduling for topical selenium agents.

Schedule 2 – Amendment

SELENIUM - Amend entry to read:

SELENIUM in preparations for human therapeutic use **except**:

(a) for topical use containing 3.5% or less of selenium sulfide;

(b) when included in Schedule 4; or

(c) for oral use with a recommended daily dose of 150 micrograms or less.

Schedule 3 – Amendment

SELENIUM – Delete entry

Schedule 4 – Amendment

SELENIUM - Amend entry to read:

SELENIUM:

(a) for human oral use with a recommended daily dose of more than 300 micrograms;

(b) for the treatment of animals:

(i) in solid, slow release bolus preparations each weighing 100 g or more and containing 300 mg or less of selenium per dosage unit;

(ii) in other divided preparations containing 30 micrograms or less of selenium per dosage unit;

(iii) as elemental selenium, in pellets containing 100 g/kg or less of selenium; or

(iv) in feeds containing 1 g/tonne or less of selenium.

Vitamin A

The Committee agreed to:

- harmonise the scheduling of Vitamin A for internal use with New Zealand on the basis of the established upper level of Vitamin A;
- recommend to New Zealand that they harmonise with Australia on topical preparations of Vitamin A because topical preparations containing 1% or less are not teratogenic and;
- adopt Retinol Equivalents as units of measurement for Vitamin A as per NHMRC recommendations.

Schedule 4 – Amendment

VITAMIN A – Amend entry to read:

VITAMIN A for human therapeutic or cosmetic use **except**:

(a) in preparations for topical use containing 1 per cent or less of vitamin A;

(b) in preparations for internal use, containing 3000 micrograms retinol equivalents or less of vitamin A; or

(c) in preparations for parenteral nutrition replacement.

1.8.1.2.3 LAXATIVES (ALOES FOR INTERNAL USE, ALOIN, BISACODYL, COLOCYNTH, IPOMOEA, JALAP RESIN, SENNOSIDES, SODIUM PICOSULPHATE)

PURPOSE

The Committee considered a Trans-Tasman Harmonisation Working Party (TTHWP) recommendation for harmonisation for laxatives (aloes for internal use, aloin, bisacodyl, colocynth, ipomoea, jalap resin, sennosides, sodium picosulphate) deferred from the June 2006 NDPSC Meeting.

BACKGROUND

The June 2006 TTHWP Meeting noted the completion of the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedules 2, 3, 4 and 8 and equivalent NZ classifications, where available. The TTHWP considered each remaining unharmonised substance and agreed that the TTHWP's recommendations be included on the agenda of the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed the recommendations from the June 2006 TTHWP Meeting and foreshadowed consideration of remaining unharmonised medicines at the October 2006 NDPSC Meeting to allow appropriate public consultation. Similarly, the Committee agreed that the recommendations to NZ to harmonise the scheduling of certain medicines should be referred to the MCC for consideration. The Committee further agreed that consideration of some substances, including laxatives (aloes for internal use, aloin, bisacodyl, colocynth, ipomoea, jalap resin, phenisatin, sennosides, sodium picosulphate), would need to be deferred to a future meeting to allow a more thorough risk and regulatory impact assessmentand that other substances would remain unharmonised at this time.

The October 2006 TTHWP meeting endorsed the recommendations and actions in relation to each medicine listed in Table 3 "Deferred harmonisation proposals" from the June 2006 NDPSC Meeting, including actions for laxatives (aloes for internal use, aloin, bisacodyl, colocynth, ipomoea, jalap resin, sennosides, sodium picosulphate). The TTHWP agreed that these actions would be tabled for consideration at the February 2007 NDPSC Meeting to allow appropriate public consultation. The Secretariat arranged to seek advice from XXXX as well as XXXX on these issues.

The October 2006 NDPSC Meeting agreed to amend the SUSDP based on the recommendations in Table 1 which was endorsed at the June 2006 meeting with minor amendments to reflect the outcome of matters discussed and agreed to at this meeting. As a consequence, a new entry for phenisatin was included in Schedule 4.

DISCUSSION

Members recalled the following from the June 2006 NDPSC Meeting:

- The Committee recalled that the June 2004 MCC Meeting recommended that the NDPSC should consider more restrictive scheduling for stimulant laxatives compared to bulk laxatives and include them in S2 to harmonise with New Zealand.
- Harmonising with NZ was expected to result in significant regulatory impact on Australian products given their unscheduled status. However, several published articles and a recent report have documented the abuse of laxatives by young people in Australia, especially by young females who have anorexia nervosa or bulimia as well as those who have body image problems.
- Adverse reactions were received on bisacodyl and senna but overall, the unscheduled status of stimulant laxatives in Australia did not give rise to safety issues from normal use.

Comment was received from XXXX commented that the XXXX have no additional information to provide on this issue as it was unaware of any issues regarding the abuse of laxatives other than those which have appeared in the medical literature and of which the medical profession is generally aware. However, XXXX commented that, given the

abuse potential for laxative agents, XXXX was surprised to find that they are currently unscheduled in Australia and that the scheduling of these products appeared to be reasonable on safety grounds.

A submission has been received from the XXXX recommending that the most appropriate Schedule for stimulant laxatives is Schedule 2. Their main points were:

- XXXX noted that the NDPSC Guidelines describe a Schedule 2 substance as one which is substantially safe in use but for which counselling is available if needed and that the substance has a low risk of masking a serious disease and an extremely low potential for abuse or harm from inappropriate use. Although unscheduled medicines are not defined within the Guidelines the assumption is that they are safer and have lower risk than Schedule 2 medicines.
- XXXX did not believe that stimulant laxatives meet the criteria for a substance which is exempt from scheduling and quote a UK journal article (Downie GD, Hind C & Kettle J; "The Abuse and Misuse of Prescribed and Over-the-Counter Medicines"; UK Hospital Pharmacist October 2000; Vol 7 242-250) regarding laxative abuse:
    - Found in approximately 4% of new hospital patients.
    - Patients are either attempting to control their weight or have an obsessional need to defecate regularly.
    - Stimulant laxatives are the most commonly abused.
    - Patients with eating disorders (eg anorexia, bulimia) who abuse laxatives do so in the false belief that this will remove food from their system and prevent absorption of calories.
    - Abuse of laxatives over time may cause abdominal cramping and pain, diarrhoea, vomiting, dehydration, metabolic acidosis, tetany and heart failure.
- Prolonged use of stimulant laxatives may also cause loss of smooth muscle tone which can result in larger and larger doses of laxatives being required for evacuation until eventually the bowel ceases to respond and constipation becomes permanent.
- XXXX noted that it has received many anecdotal reports from members about consumers with eating disorders requesting, usually large size, packs of stimulant laxatives in the false belief that it will help them lose weight. In reality these agents only remove water and food residue from the colon and, thus, only give a false weight loss. This weight returns after rehydration and is seen as weight gain which serves to reinforce the need to continue laxative use. Anecdotal reports have also indicated if such consumers are refused sale of the items they have been known to go to a nearby supermarket to obtain supply without legislative or professional restriction.
- By placing these substances in Schedule 2, supply would be restricted to pharmacy only and thus would be covered by professional guidelines and standards. Requests

for multiple packs or regular repeat sales would prompt pharmacy staff to consult a pharmacist for assistance.

- Recommendations for laxatives from GPs are often verbal and patients may be under the misapprehension that the recommendation is for long-term use. Restriction to Schedule 2 will provide the professional oversight required to clear up any misunderstanding regarding use.
- Therefore XXXX suggested that stimulant laxatives should be included in Schedule 2 in order to ensure that their supply is in accordance with Quality Use of Medicines guidelines and Trans-Tasman Harmonisation. XXXX also suggested that a restriction of all pack sizes should be considered due to their abuse potential.

A submission was received from XXXX opposing any change to the scheduling of stimulant laxatives. XXXX main points were:

- The up scheduling of stimulant laxatives would have immense regulatory implications as many of the stimulant laxatives are listed products and the up scheduling of these will force many of the products off the market as some sponsors will not be able to meet the requirements for registration.
- Some products containing sennosides are registered to allow them to be listed on the PBS. The fact that some of these products are PBS listed indicates that there remains a therapeutic need which should not be disregarded in the consideration of their scheduling status.
- As noted in the June 2006 NDPSC Record of Reasons, there are insufficient safety concerns of the current unscheduled status of stimulant laxatives to warrant them being up scheduled.
- Stimulant laxatives have been used for centuries and their safety and efficacy has been studied extensively. To date XXXX had not received any adverse event reports relating to misuse/ abuse of their product and therefore no concern had arisen regarding public safety due to misuse/ abuse of the product by patients with body image conditions such as anorexia or bulimia.
- XXXX noted that it is important to remember that body image problems are extremely complex conditions which result in a wide range of harmful health risk behaviours of which laxative abuse constitutes a very small part. Thus any consideration being given to the up scheduling should take into account that this will also restrict access to stimulant laxatives by legitimate consumers but not necessarily reduce the incidence of individuals suffering from body image disorders.
- Bulk laxatives are a category which has grown significantly over the last five years in both pharmacy and grocery and they represent a larger category than stimulant laxatives. This trend in usage shift from stimulant to bulk reaffirms that any potential public safety issues have been further minimised. XXXX also noted that both categories of laxatives are still larger in pharmacy and that consumers are adequately

warned about adverse effects from prolonged use of stimulant laxatives through the mandatory product labelling.

- XXXX maintained that the consideration being given to up scheduling these substances is unjustified given the lack of safety concerns regarding them and given the huge potential regulatory impact and that these substances should remain unscheduled.

XXXX provided a submission in which they stated that there is no support for increased regulation of hydroxyanthracene derivative laxatives (aloin, aloes for internal use and sennosides). They further stated that no conclusions could be made regarding the other substances until it is clarified what the specific identities of the ingredients referred to in the NZ Schedule of Classifications are. XXXX main points were:

- XXXX
- After consideration XXXX recommended that the existing regulatory arrangements for ingredients containing hydroxyanthracene derivatives, and used in Listed medicines, remained appropriate.
- With regard to the other stimulant laxative agents mentioned, XXXX pointed out that it is important to note these stimulant laxative ingredients are not currently scheduled in Australia when used as laxatives for the treatment of constipation. However, sodium picosulfate, and other laxative ingredients such as sodium phosphate, are subject to Schedule 3 when used orally for bowel cleansing prior to diagnostic medical or surgical procedures. XXXX also noted that laxatives regulated as OTC medicines, whether scheduled or not, must comply with the relevant guideline regarding product label warnings in the *Australian Regulatory Guidelines for OTC Medicines* (ARGOM).
- The XXXX recommendation in response to the safety review of hydroxyanthracene derivatives is likely to apply to 'aloin', 'aloes for internal use' and 'sennosides', as these substances are, or are known to contain, hydroxyanthracene derivatives. However, as 'colocynth' (if derived from *Citrullus colocynthis*), 'ipomoea' (if derived from certain *Ipomoea* species – most likely *Ipomoea jalapa* or *Ipomoea purga*), and jalap resin (if derived from *Operculina macrocarpa* Synonym *Convolvulus macrocarpus*, or possibly *Exogonium purga* Synonym *Ipomoea purga*), are not hydroxyanthracene derivatives, the recommendation made by XXXX does not apply to these laxative agents.
- There are currently 20 products containing 'colocynth' (*Citrullus colocynthis*) included in the Australian Register of Therapeutic Goods (ARTG), 15 of which are homoeopathic products. The Committee recalled that there is a general exemption in the SUSDP which allows for "any other substance included in Schedules 1 to 6, at a concentration not exceeding 10 mg per litre or 10 mg per kilogram, unless that substance is included in Schedule 7 or 8"i.e., homeopathic agents are generally not subject to the SUSDP. There are also 8 products listed as containing *Ipomoea jalapa*,

none of which are currently supplied. XXXX is currently undertaking a review of *Citrullus colocynthis* as a permitted ingredient in Listed medicines and a safety review of *Ipomoea jalapa and Ipomoea purga*. There were no products included in the ARTG containing *Operculina macrocarpa* or *Ipomoea purga*, thus if the 'jalap resin' referred to in the NZ Schedule of Classification is in fact derived from either of these species, there were currently no products that would be impacted by any change to regulatory arrangements.

- XXXX has received only one adverse drug reaction that may implicate *Citrullus colocynthis* and the WHO database records only two adverse reactions to this herb. There have been no adverse events reported for 'ipomoea' or 'jalap resin'.
- XXXX

- No new conclusions were drawn from the recent safety review of hydroxyanthracene derivatives considered by XXXX in August 2006, and no major safety concerns were identified that would necessitate the need for regulatory intervention.

XXXX provided a submission in which they stated that there are currently 24 products on the ARTG containing bisocodyl, of which 5 products are for export only. There are a total of 6 products on the ARTG containing sodium picosulfate. Of these, 3 products are indicated for the treatment of constipation. The remainder are indicated for preparation of the colon for medical procedures, making them Schedule 3 substances. XXXX also stated that they were unable to comment regarding the scheduling of these medicines as they would need to seek the advice of XXXX first.

Advice was sought from XXXX however no advice was received from this organisation. The Committee felt that this advice would be crucial to the scheduling discussion and thus, the lack of such advice made it difficult to move on the scheduling of these substances.

A Member felt that it was likely that XXXX would not oppose New Zealand's views on these issues. The Member further stated that part of the discussion is related to concerns in New Zealand about the abuse of the substances but, in general, there is a lack of evidence of this in published papers and that attempts should be made to gather such evidence. The Member stated that such evidence would be useful to help inform the Committee in its decision making.

XXXX made submissions reserving the right to comment further on any Scheduling changes made by the Committee.

Another member felt that getting information from psychiatrists, through XXXX, who treat patients with body disorder would be of benefit to the consideration of these substances. Another member noted that there is scant medical literature around this

particular issue. A Member also noted that XXXX were now stating that they do see quite lot of patient requests for the substances, most likely for purposes of abuse. The Member felt that they would like to get more evidence, rather than just anecdotal, on the prevalence of this type of behaviour. The member stated that the fact that bisacodyl is a PBS listed item with some controls around the supply of it shows that pharmacy is already dealing with the issue of abuse in some ways, but not completely.

A Member raised the point that in New Zealand, the biggest issue was that some products containing senna are being sold as dietary supplements which would be unscheduled substances in Australia. The Member stated that senna is not without problems in long term use and the Member felt that even with appropriate labelling that there could still be problems with the misuse of the substance.

It was agreed that the Committee would have to get further information from the relevant expert bodies before it could make a properly informed scheduling decision for these substances. A Member felt that the different natures of the types of stimulant laxative agents may warrant splitting the substances for consideration and not consider them as a class of substances unless there is a consistency of evidence across the different type of agents. The Member also stated that there would be known laxative substances being sold in dietary supplements in Australia as well, therefore the Member suggested hastening slowly on the issue.

A Member noted that there would be implications and significant ramifications for New Zealand if Australia did adopt a stricter scheduling of these substances as all the dietary substances in New Zealand would then be captured. It was noted that the dietary supplement industry is not regulated in New Zealand, therefore it will be very difficult to garner information. A Member suggested that eating disorders groups may have information on where their clients are obtaining their supply of the substances from (i.e., are they obtaining the substances from supermarkets and thus using the dietary supplements exemption, or are they obtaining them from pharmacy.)

OUTCOME

The Committee agreed to defer consideration of the scheduling of stimulant laxatives (aloes for internal use, aloin, bisacodyl, colocynth, ipomoea, jalap resin, sennosides, sodium picosulphate) to the June 2007 NDPSC Meeting in order to allow further advice to be sought from relevant expert bodies such as XXXX. The Committee also thought it may be useful to seek input on the incidence of abuse of laxatives by eating disorder patients and perhaps from XXXX. With the input from all these bodies, the Committee will be able to make a more informed decision on the appropriate scheduling of stimulant laxatives.

1.8.1.2.4 MEDICINES IN SCHEDULES 5, 6 OR 7 WHICH ARE IN A NEW ZEALAND MEDICINES CLASSIFICATION – NICOTINE, PICRIC ACID, PYRETHRINS, SODIUM HYDROXIDE, TAR AND XYLENOLS

PURPOSE

The Committee considered harmonisation proposals for a number of medicines included in Schedules 5, 6 or 7 that are currently in an unharmonised New Zealand medicines classification.

BACKGROUND

The June 2006 TTHWP Meeting noted the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedules 2, 3, 4 and 8 and equivalent New Zealand classifications, where available. The TTHWP considered each remaining unharmonised substance and agreed on recommendations to be tabled at the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed the TTHWP's recommendations and foreshadowed consideration of the majority of the remaining unharmonised medicines at the October 2006 NDPSC Meeting to allow public consultation. Similarly, the Committee agreed that the recommendations to New Zealand to harmonise the scheduling of certain medicines should be referred to the MCC for consideration. The Committee also agreed that some substances would have to remain unharmonised at this time. The Committee further agreed to defer consideration of some substances to a future meeting to allow a more thorough risk and regulatory impact assessment.

The October 2006 TTHWP Meeting endorsed a number of recommendations in relation to those substances deferred from the June 2006 NDPSC Meeting, set out in TTHWP's Table 3. This table included proposed actions for some medicines currently included in Schedules 5, 6 or 7 (nicotine, picric acid, pyrethrins, sodium hydroxide, tar and xylenols). The TTHWP agreed to table these actions for consideration at the February 2007 NDPSC Meeting.

DISCUSSION

General pre-meeting comments were received from XXXX and XXXX noting an interest in this item. XXXX also noted that changes to the scheduling of the nominated substances may have significant impacts for industry, distribution, and users of products. XXXX asserted that it was not aware of specific considerations, by NDPSC, for the individual nominated substances [the Committee noted that the pre-meeting gazette clearly referenced the harmonisation table from the June 2006 NDPSC Meeting].

Nicotine

Members noted the following from the June 2006 NDPSC Table 3.

- Nicotine as an aid in withdrawal from tobacco smoking was essentially harmonised (not including New Zealand's allowances for smoking cessation clinics).
- Medicines containing nicotine which were not for smoking cessation were unharmonised. In New Zealand these were classified as Prescription Medicines. In Australia they were Schedule 7 unless in Schedule 6 (≤ 3%, for treatment of animals).

The Committee considered TTHWP's proposal to harmonise with the current New Zealand entries. Members noted a suggestion that this could be achieve by amending the Schedule 4 entry to also capture "for other human therapeutic use" and to exempt human therapeutic use from the Schedule 7 entry.

The TTHWP requested that the Secretariat investigate reports of nicotine products indicated for the treatment of Crohn's disease which are not captured in the current Schedule 4 entry for nicotine. Members noted the following.

- The Centre for Digestive Diseases (CDD) website noted that there was currently research into a number of treatments for ulcerative colitis (a Inflammatory Bowel Disease (IBD) related to Crohn's disease), including use of nicotine. In an early study, symptoms improved in some patients who were given nicotine through a patch or an enema. The CDD advised that nicotine use as treatment was still experimental.
- Another website (Smokingguts) noted:
    - it has been established through research that there is a connection between IBD and cigarette smoking. However, smoking seems to have opposite effects on the two main forms of IBD - ulcerative colitis and Crohn's disease;
    - nicotine in tobacco cigarettes apparently has a positive influence on symptoms of ulcerative colitis. It is theorized that the nicotine affects the smooth muscle inside the colon. This affect may alter gut motility, which is the rate at which waste moves through the colon;
    - smoking cigarettes actually has an inverse effect on Crohn's disease; people who smoke, or who have smoked in the past, have a higher risk of developing Crohn's than non-smokers. Crohn's Disease patients that smoke have an increased number of relapses, repeat surgeries, and aggressive immunosuppressive treatment. People with Crohn's are generally encouraged to stop smoking by their physicians in order to prevent flare-ups of the disease.

A pre-meeting comment was received from XXXX regarding nicotine. XXXX supported the amendment proposed by the TTHWP in Table 3.

Picric acid

Picric acid is the synonym for trinitrophenol (which is the AAN). Picric acid burns readily and explodes when heated rapidly or when subjected to percussion. It has disinfectant properties and was formerly used in the treatment of burns. It is now chiefly used in manufacturing industries and as a laboratory agent.

Members noted the following from the June 2006 NDPSC Table 3.

- Picric acid is classified as general sale in NZ.
- Picric acid in concentrations > 5% is Schedule 6 in Australia (excluding derivatives).

The TTHWP requested that the Secretariat investigate the types of products containing picric acid and if indeed there were medicines containing this substance or if picric acid was used therapeutically. TTHWP proposed that if there were no products but picric acid was used therapeutically for humans, to include a primary entry in Schedule 4 as per policy and recommend both countries to harmonise. Members also considered replacing picric acid with the AAN, trinitrophenol.

Members noted that the Secretariat had investigated the uses of picric acid and advised that picric acid was historically used as an antiseptic, or astringent, and bottles of picric acid or gauze burn dressing containing picric acid are often found in first aid kits dating from the 1930-1940s or earlier. However, due to picric acid's highly explosive nature it no longer appears to be used in therapeutics. A search of the ARTG under trinitrophenol only located two homeopathic products contained this ingredient (below the 10 mg/L general exemption cut-off). There were no medicines listed in SMARTI containing trinitrophenol (or picric acid), as either an excipient or an active ingredient.

The Committee also noted the following from picric acid's scheduling history.

- The current Schedule 6 entry was introduced at the February 1971 Meeting.
- The August 1991 DPSSC Meeting considered cut-offs for a range of scheduled poisons identified by homoeopathy interests as being used in the practice of homoeopathy and agreed to include a 0.01% cut-off for picric acid in the proposed Appendix G.
- The May 1992 DPSSC Meeting considered comments on the proposed Appendix G and was unable to determine a cut-off level for a number of substances, including picric acid, due to inadequate data.
- The February 2000 NDPSC Meeting considered a TTHWP recommendation that NZ should delete picric acid from Part III of the medicines regulations. Members noted:
    - The TTHWP considered whether to adopt a Schedule 2 position with a recommendation to NZ for a 5% cut-off. This option was not accepted on the grounds that there were no Australian registered products and the drug was

outmoded therapeutically. It was unlikely that NZ had products either. There appeared to be no justification for its retention for human therapeutic use.

- Hence it was recommended that picric acid be deleted from Part III and that it be brought to the attention of ERMA under the HSNO Act because of its physical properties.

Members also noted the following from the Micromedex entry for trinitrophenol.

- Trinitrophenol has disinfectant properties and was formerly used in the treatment of burns. It is now chiefly used in manufacturing and as a laboratory reagent.
- Dermatitis, skin eruptions, severe itching and yellow staining of the skin may occur following contact with trinitrophenol. Systemic toxicity may follow ingestion or absorption through the skin or lungs; symptoms may include vomiting, pain, and diarrhoea, progressing to haemolysis, hepatitis, anuria, convulsions, unconsciousness, and death. The metabolic rate is increased, causing pyrexia.
- Trinitrophenol has been used in homoeopathy.

Pyrethrins

Members noted the following from the June 2006 NDPSC Table 3.

- Pyrethrins are general sale in NZ.
- Naturally occurring pyrethrins are Schedule 5 in Australia, with an exception cut-off of ≤ 10%.

TTHWP recommended that the Committee consider inclusion of a primary entry in Schedule 2 with an exemption for preparations containing ≤ 10%, with New Zealand to consider harmonising with this entry.

The TTHWP had also requested a Secretariat investigation as to whether there were products on ARTG and SMARTI. A search of ARTG under pyrethrin located: 4 products containing pyrethrins; 3 containing pyrethrin I (based on chrysanthemic acid); and 4 containing pyrethrin II (based on pyrethric acid). The strongest concentration found was 0.2% in head lice treatments. A search of SMARTI revealed three head lice products, 2 containing pyrethrins up to 0.2 % and 1 containing up to 2%.

Sodium Hydroxide

Members noted the following from the June 2006 NDPSC Table 3/

- Sodium hydroxide is classified as general sale in NZ.
- Sodium hydroxide in Australia is Schedule 6 for > 5% and Schedule 5 for ≤ 5% with a pH > 11.5 and exempt for preparations ≤ 5% with a pH ≤ 11.5.

TTHWP has suggested that the unharmonised status could be addressed by including an exception for therapeutic use. TTHWP had identified both disinfectants and dental restorative materials containing sodium hydroxide on the ARTG. Sodium hydroxide is also present as an excipient in a very large number of products, often to correct pH.

Tar and Xylenols

Members noted the following from the June 2006 NDPSC Table 3.

- Tar and xylenols are classified as general sale in NZ.
- Tar acids, distilling within the range 230 -290°C inclusive, are Schedule 6 in Australia. Cresols, tar and xylenols boiling below 220°C are captured in the current Schedule 2 phenols entry (with an exception for external use preparations containing ≤ 3%). There is also a Schedule 4 phenol entry covering preparations for injection.

TTHWP suggested that New Zealand consider harmonisation with Australia at the February 2007 meeting and include tar, and xylenols as part of the phenol and cresol recommendation. Members recalled that at the October 2006 NDPSC Meeting, under cresols in Table 2, it was recommended that New Zealand consider harmonising with the Schedule 2 and 4 entries for phenol. It was also recommended that Australia include a cross-reference for cresol to phenol in the SUSDP index (this action was inadvertently overlooked at the October 2006 NDPSC Meeting).

OUTCOME

Sodium Hydroxide

The Committee agreed that the current scheduling status of sodium hydroxide remains appropriate, and is essentially harmonised with New Zealand.

Cresol, Tar, Xylenol

The Committee agreed to:

- include a cross-reference for cresol, tar and xylenol to phenol in the SUSDP index; and
- recommend to New Zealand that it consider replacing the current tar and xylenols general sale classifications by harmonising with the current Schedule 2 and 4 phenol entries.

DECISION 2007/49 - 4

Nicotine

The Committee agreed that:

- the current scheduling of nicotine for all uses apart from human therapeutic use remains appropriate; and
- human therapeutic use of nicotine when not an aid in withdrawal from tobacco smoking should be captured by Schedule 4 on the grounds of harmonisation.

Schedule 4 – Amendment

NICOTINE – Amend entry to read:

NICOTINE in preparations for human therapeutic use **except**:

(a) when included in Schedule 2; or

(b) for use as an aid in withdrawal from tobacco smoking in chewing gum, lozenges, or preparations for sublingual or transdermal use.

Schedule 7 – Amendment

NICOTINE – Amend entry to read:

NICOTINE **except**:

(a) when included in Schedule 6;

(b) in preparations for human therapeutic use; or

(c) in tobacco prepared and packed for smoking.

Picric Acid (Trinitrophenol)

The Committee agreed to include a primary entry for trinitrophenol for human therapeutic use in Schedule 4 (along with a cross reference for picric acid) and recommended that New Zealand consider harmonising with this decision. The Committee also agreed to amend the Schedule 6 entry to also use the synonym trinitrophenol.

Schedule 4 – New Entry

TRINITROPHENOL (excluding its derivatives) in preparations for human therapeutic use.

Schedule 6 – Amendment

TRINITROPHENOL - Amend entry to read:

TRINITROPHENOL (excluding its derivatives) **except**:

(a) in preparations for human therapeutic use; or

(b) in preparations containing 5 per cent or less of trinitrophenol.

SUSDP 23 Index – New Entry

PICRIC ACID
See trinitrophenol.

Pyrethrins

The Committee agreed:

- to include a primary entry for naturally occurring pyrethrins for human therapeutic use in Schedule 2;
- that preparations containing 10% or less of naturally occurring pyrethrins pose little risk to the public and warrant exemption from the requirements of scheduling; and
- to recommend harmonisation on this decision to New Zealand.

Schedule 2 – New Entry

PYRETHRINS, naturally occurring, being pyrethrolone, cinerolone or jasmolone esters of chrysanthemic or pyrethric acids, for human therapeutic use in preparations containing more than 10 per cent of such substances.

Schedule 5 – Amendment

PYRETHRINS – Amend entry to read:

PYRETHRINS, naturally occurring, being pyrethrolone, cinerolone or jasmolone esters of chrysanthemic or pyrethric acids **except**:

(a) in preparations for human therapeutic use; or

(b) in preparations containing 10 per cent or less of such substances.

1.8.1.2.5 OTHER DEFERRED HARMONISATION PROPOSALS - KETOPROFEN, MEPTAZINOL, PYRITHIONE ZINC

PURPOSE

The Committee considered TTHWP recommendations for harmonisation regarding ketoprofen, meptazinol and pyrithione zinc deferred from the June 2006 NDPSC Meeting.

BACKGROUND

The June 2006 TTHWP Meeting noted the completion of the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedules 2, 3, 4 and 8 and equivalent NZ classifications, where available. The TTHWP considered each remaining unharmonised substance and agreed to recommendation that were tabled at the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed the TTHWP recommendations and foreshadowed consideration of remaining unharmonised medicines at the October 2006 NDPSC Meeting to allow appropriate public consultation. Similarly, the Committee agreed that the recommendations to NZ to harmonise the scheduling of certain medicines should be referred to the MCC for consideration. The Committee further agreed that consideration of some substances, including ketoprofen, meptazinol and pyrithione zinc, would need to be deferred to a future meeting to allow a more thorough risk and regulatory impact assessment.

The October 2006 TTHWP meeting endorsed the recommendations and actions in relation to each medicine listed in Table 3 from the June 2006 NDPSC Meeting, including actions for ketoprofen, meptazinol and pyrithione zinc. It was agreed that these recommendations would be considered at the February 2007 NDPSC Meeting to allow appropriate public consultation.

DISCUSSION

Member's noted a pre-meeting comment from XXXX asserting that scheduling changes for the nominated substances may have significant impacts for industry, distribution, and users of products. XXXX also asserted that it was not aware of specific considerations, by NDPSC, for the individual nominated substances [Members noted that the pre-meeting gazette clearly referenced the harmonisation table from the June 2006 NDPSC Meeting].

Ketoprofen

Members noted the following from the June 2006 NDPSC Table 3.

- Ketoprofen in preparations for dermal use are exempt from scheduling in Australia, while in New Zealand it is external use of ketoprofen which is classified as General Sale. All other presentations of ketoprofen are essentially harmonised.
- The TTHWP noted that there were no ophthalmic products on New Zealand's SMARTI data base. The Secretariat was asked to investigate whether there were any ophthalmic preparations on the ARTG. [The Secretariat confirmed that there appear to be no ophthalmic products on the ARTG]
- The TTHWP recommended that, should there be no current ophthalmic products, New Zealand consider harmonising with Australia.

Members noted the following from XXXX pre-meeting comment.

- XXXX asserted that this item raised the broader issue of harmonisation of definitions. The process of harmonising will be enhanced by ensuring consistency of definitions.
- XXXX noted the following New Zealand definition of 'external':

  "For external use, in relation to any medicine or related product, means for application to the anal canal, ear, eye, mucosa of the mouth, nose, skin, teeth, throat, or vagina, where local action only is required and where extensive systemic absorption will not occur; but nothing in these regulations relating to medicines or related products intended for external use shall apply to nasal drops, nasal inhalations, nasal sprays, teething applications, throat lozenges, throat pastilles, throat sprays, or throat tablets."
- Thus the New Zealand General Sale category includes products that would be considered prescription medicines in Australia. However, XXXX noted that it appears that, in New Zealand, ketoprofen suppositories are available as prescription medicines. This appears to be contrary to the General sale entry capturing external use. [Members noted that suppositories are not for local action only, and that this is why suppositories remain Prescription Medicines in New Zealand].
- There appears to be no reason for maintaining different schedule entries in Australia and New Zealand.

Meptazinol

Members noted the following from the June 2006 NDPSC Table 3.

- Meptazinol is currently unscheduled in Australia. However, it is classified as a Prescription Medicine in New Zealand.
- The TTHWP noted that meptazinol had potential for abuse. There were no products on ARTG, and that there had been one prescription 200 mg tablet with registration withdrawn on SMARTI.
- The TTHWP recommended that Australia consider harmonising with New Zealand.

Members also noted the following from the Martindale monograph for meptazinol.

- Meptazinol is a mixed opioid agonist and antagonist with partial opioid agonist activity at the 1 opioid receptor; it also has cholinergic activity. Meptazinol is used in the treatment of moderate to severe pain. It has a shorter duration of action than morphine.
- In assessing the dependence potential of meptazinol, a WHO expert committee noted that abrupt discontinuation of chronic meptazinol use precipitated only slight withdrawal signs in animals and that meptazinol did not suppress opioid withdrawal signs/symptoms in morphine dependent humans. Abuse had not been reported. They considered the likelihood of abuse was moderate and that international control was not warranted.
- Meptazinol is claimed to have a low incidence of respiratory depression. There have been occasional reports of psychiatric disorders such as hallucinations, confusion, and depression. Meptazinol has the potential to precipitate withdrawal symptoms if given to patients who are physically dependent on opioids.

Pyrithione zinc

Members noted the following from the June 2006 NCPSC Table 3.

- The Schedule 2 pyrithione zinc entry captures all human therapeutic use except shampoos with < 2% (when compliant with RASML) or in semi-solid hair preparations. However, the New Zealand pyrithione zinc Pharmacy Only entry captures all medicines containing > 2%. (Therefore semi-solid hair preparations with >2% are only captured in New Zealand, and human therapeutic use < 2% (which is not an exempted hair preparation) is only captured in Australia.)

  [Members noted that the June 2006 NDPSC Table 3 omitted the New Zealand General Sale entry for pyrithione zinc which reads “for external use in medicines containing 2% or less”. It also omitted the Australian Schedule 6 entry which

captures pyrithione zinc except when for human use or when immobilised in solid preparations containing ≤ 0.5%.]

- The TTHWP has recommended that New Zealand consider harmonisation with Australia. It was noted that a New Zealand representative had expressed a preference for the wording "for the treatment of the scalp" as opposed to specifying the formulations.
- The TTHWP also requested that the Secretariat investigate the rationale for restricting the exemption to semi-solid hair preparations and shampoo.

Members noted Secretariat advice that it had located the following from past NDPSC Minutes regarding the rationale for restricting the Schedule 2 exemption to semi-solid hair preparations and shampoo (< 2%).

- The December 1965 PSC Meeting agreed to include a pyrithione zinc entry in Schedule 2 following consideration of a anti-dandruff cream containing 0.48% pyrithione zinc.
- An application requesting a 2% cut-off for shampoo's containing pyrithione zinc was considered at the February 1967 PSC Meeting. On the evidence submitted the Committee was of the opinion that such preparations should not be released to the public without some warning label. The Committee therefore recommended:
  - Amending the Schedule 2 to only capture > 2% pyrithione zinc.
  - Creation of a Schedule 5 entry for ≤ 2% pyrithione zinc with an exemption if labelled/packed in the specified manner.
- The August 1985 DPSSC Meetings considered data which indicated that considerable eye irritation had been demonstrated. The Members also reviewed the specific labelling required for the Schedule 5 exemption. The Committee subsequently agreed to delete the Schedule 5 entry and amend the Schedule 2 entry to capture pyrithione zinc for human use except in preparations containing ≤ 2% pyrithione zinc, when:

  (a) in semi-solid hair preparations; or

  (b) in shampoos labelled with either of the statements "keep out of eyes" or "if in eyes, rinse well with water".
- The November 1988 DPSSC Meeting amended the above decision so that the 2% cut-off and specified labelling only applied to shampoos, and the exemption for semi-solid hair preparations became a general exemption with no labelling of concentration requirements. No record was located to indicate why the exemption for semi-solid hair preparations was broadened.
- Subsequent considerations of pyrithione zinc were focused on the development of the Schedule 6 entry covering non-human use. Members noted, however, that the August 2000 NDPSC consideration of this issue included a review of toxicity data for pyrithione zinc including:

- Acute toxicity data for pyrithione zinc:

Worst oral LD_{50} (rats)	221 mg/kg bw (females)
Worst oral LD_{50} (other species)	>1000 mg/kg bw in monkeys (0/2 deaths)
Worst dermal LD_{50}:	>2000 mg/kg bw in rats (2/10 deaths)
Worst inhalational LC_{50}:	>610 mg/m^3 in rats (4 h nose-only exposure; 3/10 deaths); 140 mg/m^3 (4 h whole-body exposure) in rats
Skin irritation:	Non-irritant in rabbits
Eye irritation:	Corrosive in rabbits
Skin sensitisation:	Not a sensitiser in guinea pigs (Buehler method) or humans (patch test)
T-value:	20
NOEL:	0.5 mg/kg bw/day in a 2-year chronic study and a 2 generation reproduction study in rats

- It was noted that although pyrithione zinc has very low solubility (around 4-6 ppm), it was the soluble component rather than the insoluble particles which were responsible for the ocular effects. This was based on the observation of irreversible corneal damage after only a 30 second exposure.
- It was noted that almost no dermal irritation occurred even after daily exposure to approximately 1g/kg/day for a month. However pyrithione zinc was particularly active against mucous membranes, with oral administration resulting in corrosion to the mucous membranes of the gastro-intestinal tract.
- It was noted that two ocular test results were obtained for a product containing 3-5% pyrithione zinc. Using 100 µL in a standard eye irritation assay, severe to corrosive eye irritation resulted. However, in a low volume eye irritation assay, the effect was moderate to severe eye irritancy. The evaluator concluded that on the basis of the data held on pyrithione zinc, corrosive eye irritancy would be likely to occur down to concentration as low as 0.3%.
- Having considered the issues, the Committee agreed that zinc pyrithione, other than for human therapeutic use to which a Schedule 2 entry and certain exemptions applied, should be included in Schedule 6 of the SUSDP. The decision was based on the acute toxicological profile of pyrithione zinc, in particular its acute oral toxicity and severe eye irritancy/corrosivity.
- The October 2005 NDPSC Meeting, as part of consequential amendments to the SUSDP for consistency with the RASML, amended the Schedule 2 entry to give the current wording.

A pre-meeting comment was received from XXXX which supported adoption of the New Zealand schedule i.e. broadening the Australian exemption from semi-solid hair preparation and shampoos to permit other topically applied preparations for local effect.

OUTCOME

Ketoprofen

The Committee agreed to recommend to New Zealand that it consider harmonising with Australia by amending its general sale classification for ketoprofen from "external use" to "dermal use".

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Meptazinol

The Committee agreed to include meptazinol in Schedule 4 on the grounds of harmonisation and that appropriate use of this medicine would require professional diagnosis and management.

Schedule 4 – New entry

MEPTAZINOL.

Pyrithione Zinc

The Committee agreed to:

- amend the Schedule 2 entry for pyrithione zinc by referring to "for treatment of the scalp" as opposed to specifying semi-solid or shampoo preparations;
- therefore limit the existing semi-solid preparations exemption to ≤ 2% pyrithione zinc when compliant with RASML;
- recommend to New Zealand that it consider harmonising with this decision; and
- amend the Schedule 6 pyrithione zinc entry exemptions for consistency with the changes to the Schedule 2 entry.

Schedule 2 – Amendment

PYRITHIONE ZINC – Amend entry to read:

PYRITHIONE ZINC for human therapeutic use, **except** in preparations for the treatment of the scalp containing 2 per cent or less of pyrithione zinc when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*.

Schedule 6 – Amendment

PYRITHIONE ZINC – Amend entry to read:

PYRITHIONE ZINC **except**:

(a) when included in Schedule 2;

(b) in preparations for the treatment of the scalp containing 2 per cent or less of pyrithione zinc when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*; or

(c) when immobilised in solid preparations containing 0.5 per cent or less of pyrithione zinc.

1.8.1.3.2 CADMIUM COMPOUNDS INCLUDING CADMIUM SULPHIDE

PURPOSE

The Committee considered the scheduling of cadmium compounds including cadmium sulphide.

BACKGROUND

The February 1970 PSC Meeting agreed to include preparations containing ≤ 2.5% of cadmium sulphide for human therapeutic use in Schedule 5. Members also agreed to include a parent entry for all other cadmium salts and compounds in Schedule 6 due to toxicity.

The February 1988 DPSSC Meeting noted that animal studies had shown an association between cadmium exposure and a variety of tumours. Human epidemiological studies indicated an increase in lung cancers as a result of occupational exposure to cadmium. Cadmium is acutely toxic at low doses and in animal tests cadmium produced embryotoxicity, foetotoxicity and teratogenicity. The major use in Australia at the time was in the electroplating industry and other industrial products and applications. The Meeting agreed to maintain the Schedule 6 entry and to request that no domestic agvet products be registered. This decision was confirmed by the May 1988 DPSSC Meeting.

The August 2000 NDPSC Meeting considered the issue of consistency between the schedule entries and Appendix I "Uniform Paint Standard". The Committee agreed to include an exemption from the Schedule 6 cadmium compounds entry for paints and tinters containing ≤ 0.1% cadmium.

DISCUSSION

Members noted that a search of the ARTG located only a single product containing cadmium sulfide (and no products containing cadmium). Cadmium sulfide, 0.044%, was listed as an excipient in a medical device - a dentine adhesive. This device did not qualify for the general Appendix A medical devices exemption as it was not a Class III device. However, the product did appear to qualify for the general exemption for medical and veterinary adhesives, glues and cements.

Members also noted that the Micromedex entry for cadmium sulfide provided the following:

- Cadmium sulfide is a dermatological agent and antiseborrheic.
- Cadmium sulfide releases toxic hydrogen sulfide upon contact with water or acids.
- Cadmium sulfide is used in photoconductors, dandruff shampoos, pigments and phosphors, electronic components, and in solar cells.
- Acute clinical effects:
    - No studies were found for acute exposure to cadmium sulfide in humans. It is not acutely toxic in experimental animals (RTECS), and is generally regarded as being less toxic than more soluble cadmium compounds.
    - Acute inhalation of cadmium and its salts can cause pulmonary oedema; fatal in approximately 20% of cases. Ingestion of cadmium or its salts produces immediate gastrointestinal distress with pain, nausea, vomiting, diarrhoea, excessive salivation, muscular cramps, and signs of CNS depression (such as dizziness, weakness, headache, cardiovascular collapse, and shock), and death.
- Chronic clinical effects:
    - Cadmium sulfide is relatively inert for causing lung damage in chronic inhalation exposure. Some cases of emphysema have been reported, but only after at least 25 years of exposure. Kidney injury with proteinuria has developed following chronic exposure to cadmium sulfide.
    - In a 30-day rat inhalation study, cadmium sulfide was absorbed only one-tenth as much as cadmium chloride or cadmium oxide.
    - If cadmium sulfide is being used under conditions where cadmium fumes may be generated, inhalation exposure might cause metal fume fever, a flu-like condition involving fever, chills, sweating, aches and pains, and difficulty breathing. Symptoms of metal fume fever generally appear within hours of exposure and subside within 24 to 48 hours, leaving no permanent effects.
    - IARC (2004) listed cadmium sulfide as carcinogenic to humans (rating 1). In animal studies, cadmium sulfide was carcinogenic in rats. It is relatively insoluble; tumours developed at the site of injection. Cadmium sulfide caused

broken chromosomes in cultured human cells and also caused in vitro transformation of hamster cells.

- Cadmium caused birth defects in several species of laboratory animals and was embryotoxic and fetotoxic. There was some evidence that cadmium may be a human reproductive hazard. There had been isolated cases of impotence and microscopic changes in the testes of men working with cadmium.

Members were advised that cadmium was not currently listed in the *Required Advisory Statements for Medicines Labels* (RASML).

Pre-meeting comments were received from XXXXXXXX and the XXXXXXXX noting an interest in this item.

The Members generally agreed that cadmium sulfide for human therapeutic use should be removed from Schedule 5. Noting the toxicity of cadmium compounds the Committee discussed whether to include a parent entry in Schedule 4 for human therapeutic use (with an exemption to allow excipient use of cadmium sulfide below 0.1% which appears to present little risk). Members considered the following proposed scheduling changes:

Schedule 4 – New Entry

CADMIUM COMPOUNDS for human therapeutic use **except** in preparations containing 0.1 per cent or less of cadmium sulfide as an excipient.

Schedule 5 – Amendment

CADMIUM SULPHIDE – Delete entry.

Schedule 6 – Amendment

CADMIUM COMPOUNDS **except**:

(a) for human therapeutic use; or

(b) in paints or tinters containing 0.1 per cent or less of cadmium calculated on the non-volatile content of the paint or tinter.

The Committee was advised that while cadmium sulphide had been include in the February 2007 pre-meeting gazette notice, cadmium compounds had not, so any decision for cadmium compounds would need to be foreshadowed. Additionally, a Member noted that a list of possible human therapeutic use patterns for cadmium compounds would aid in considering the scheduling of these substances. The Committee therefore agreed to foreshadow the scheduling of cadmium compounds for human therapeutic use at the June 2007 NDPSC Meeting.

Members were also advised by the Secretariat that 'sulphide' was used 3 times in the SUSDP (cadmium sulphide, carbon disulphide, hydrogen sulphide) and that the alternative spelling, sulfide, was also used 3 times (selenium sulfide, potassium sulfide, sodium sulfide). It was noted that sulfide is traditionally spelled 'sulphide' in British english, but IUPAC has adopted the spelling "sulfide", as has the Royal Society of Chemistry Nomenclature Committee. A proposal to editorially amend the carbon disulphide and hydrogen sulphide entries for consistency was presented in item 21.1.1.

OUTCOME

The Committee agreed to foreshadow consideration of cadmium compounds, including cadmium sulfide, for human therapeutic use at the June 2007 NDPSC Meeting.

1.8.1.4 POST-MEETING COMMENT ON THE OCTOBER 2006 HARMONISATION DECISION – QUATERNARY AMMONIUM COMPOUNDS, ALENDRONIC ACID, COBALT, ETHYLHEXANEDIOL, HEXOPRENALINE, NICOTINIC ACID, POTASSIUM CHLORIDE, RIFAMYCIN, THYROTROPIN-RELEASING FACTOR, VECURONIUM, VIPRYNIUM (PYRVINIUM), VITAMIN D

PURPOSE

The Committee considered post-meeting comment regarding the October 2006 NDPSC harmonisation decisions (2006/48-1, -14 and -16).

BACKGROUND

The June 2006 TTHWP Meeting noted the completion of the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedule 2, Schedule 3, Schedule 4 and Schedule 8 and equivalent New Zealand classifications. The TTHWP considered each remaining unharmonised substance and agreed to present a number of recommendations at the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed these recommendations (recorded in Table 1 from the June 2006 NDPSC Meeting) and agreed to foreshadowed these for consideration at the October 2006 NDPSC Meeting to allow appropriate public consultation.

The October 2006 NDPSC Meeting agreed to amend the SUSDP based on the above recommendations (with minor amendments to reflect the outcome of matters discussed and agreed to at the October 2006 NDPSC Meeting).

DISCUSSION

XXXX forwarded a number of comments from XXXX regarding several of the October 2006 NDPSC harmonisation decisions (2006/48-1, -14 and -16). These comments were circulated to the Drafting Advisory Panel (DAP) prior to the February 2007 NDPSC Meeting. Members noted that the suggestions from XXXX, followed by relevant DAP considerations, included:

Quaternary Ammonium Compounds

Many of the Schedule 4 amendments involve quaternary ammonium compounds. It was asserted that a characteristic of these compounds was that they cannot exist as free substances – only as salts. It was therefore asserted that it would be more accurate if the Schedule 2 and 4 entries for quaternary ammonium compounds referred to their salts. In addition it was noted that the amendment to the vecuronium entry had inadvertently been spelt "vercuronium".

- XXXX DAP comments – Endorsed confirming the October 2006 NDPSC decision to schedule the parent compound rather than the salt with regard to quaternary ammonium compounds. Also endorsed the proposal to correct the spelling of "vercuronium".
- Additional XXXX comment – The Member asserted that it was not necessarily illogical for a scheduled base substance to not exist per se in a free state. In some cases it could be the most convenient way of capturing all derivatives.
- Additional XXXX comment – The Member was concerned that any move to specify salts in the quaternary ammonium compounds entries would then exclude all other derivates. The Member proposed to leave the entries as is, as all derivatives, including the salts, would be captured.

The Committee agreed to confirm the October 2006 decision and to correct the spelling of vecuronium.

Alendronic acid

An entry for alendronic acid already appears in Schedule 4. It would be more appropriate to delete the existing entry for alendronate sodium than to replace it with a duplicate entry for alendronic acid.

- XXXX DAP comment – all agreed with the proposal.

The Committee agreed with the proposal.

Cobalt

Edetic acid is currently in Schedule 4 with an exemption for dicobalt edetate in preparations for the treatment of cyanide poisoning. It was asserted that this exemption would be nullified unless a similar exemption was included in the new Schedule 4 entry for cobalt for therapeutic use.

- XXXX DAP comment – all agreed with the proposal.

The Committee noted advice from a Member that the entry should capture human therapeutic use rather than therapeutic use, as there was a wide range of cobalt agvet products for which Schedule 4 restrictions were unnecessary. The Committee agreed to vary the October decision to capture only human therapeutic use with a dicobalt edetate exemption.

Ethylhexanediol

An entry for human use already appears in Appendix C. It was asserted that the proposed new entry in Schedule 4 for ethanehexanediol (sic ethylhexanediol) would conflict with the Appendix C entry.

- XXXX DAP comment – The Appendix C entry for ethylhexanediol is for human use and the Schedule 4 entry may only be intended to pick up the animal use.

The Committee agreed that the Schedule 4 entry was only intended to capture animal therapeutic use, and that it remained appropriate for human therapeutic use to be captured by Appendix C.

Hexoprenaline

An entry already appears in Schedule 4. The proposed new entry should be deleted.

- XXXX DAP comment – all agreed with the proposal.

The Committee also agreed with the proposal.

Nicotinic Acid

Asserted that the new entry in Schedule 4 would cause a problem as preparations excepted from Schedule 3 will default to Schedule 4 unless the Schedule 3 exemptions are repeated in the Schedule 4 entry.

- XXXX DAP comment – all agreed with the proposal.

The Committee agree to replicate the Schedule 3 exemptions in the new Schedule 4 entry.

Potassium Chloride

The first exemption clause has been raised from 100 mg per dosage unit to 600 mg per dosage unit. This will exempt all potassium chloride tablets currently available. Was this intended?

- XXXX DAP comment – This could be further considered by the NDPSC.
- XXXX DAP comment – Noted that the Committee appeared to decide on the 600mg cut-off based on the strength of XXXX tablets. The Member questioned whether he was the only one who assumed that XXXX and XXXX would also become Schedule 4. They contain 596 mg of potassium chloride, making them unscheduled, even though with their additional potassium carbonate and bicarbonate they contain much more potassium than XXXX which is Schedule 4. As it is potassium rather than chloride which is the toxic element of concern, it seems it would make more sense to schedule on the basis of the elemental potassium content as New Zealand does. The Member suggested that this go to the Committee.

Members noted that the October 2006 NDPSC Meeting consideration of potassium chloride included a discussion of the merits of a potassium chloride entry vs. an elemental potassium content entry. The Members discussed whether there was a need to vary the cut-off from 600 mg, and concluded that the Committee had insufficient evidence before it to justify a cut-off change at this time. Members therefore agreed to confirm decision 2006/48-14 to include potassium chloride in Schedule 4 with a 600mg cut-off. The Committee also agreed to foreshadow consideration at the June 2007 NDPSC Meeting of a reduction in the cut-off for the Schedule 4 potassium chloride entry. The Members agreed that the pre-meeting gazette notice would include a specific proposed cut-off based on a Secretariat review of products on the ARTG.

Rifamycin

Rifamycin already appears as an alternative name in the entry for rifampicin, and it was asserted that it would be covered by the proposed amended entry for rifampicin and therefore the proposed new entry for rifamycin should be deleted.

- XXXX DAP comment – Suggested putting the INN in the Schedule entry and putting the alternative name as a cross-reference in the index, rather than having two separate Schedule entries. The Member asserted that rifampicin is a type of rifamycin, or at least a closely related derivative of rifamycin.
- XXXX DAP comment – Supported separate entries for rifamycin and rifampicin as they have separate monographs in Martindale and substantially different molecular weights. The Member asserted that separate listing makes the Committee's intention clearer.
- XXXX DAP comment – Noted that the separate entries for rifamycin and rifampicin were deliberate.

The Committee noted that both rifamycin and rifampicin were INNs. The Committee agreed to confirm the October 2006 decision.

Thyrotropin-releasing Factor

An entry for "PROTIRELIN (thyrotrophin releasing factor)" already appears in Schedule 4. It was asserted that the proposed new entry for thyrotropin-releasing factor was an unnecessary duplication of the existing entry.

- XXXX DAP comment – This appears to be deliberate and could be resolved by removing the bracketed words following protirelin and retaining the new entry for thyrotropin-releasing factor.
- XXXX DAP comment – Suggested putting the INN (protirelin) in the Schedule entry and putting the alternative name as a cross-reference in the index, rather than having two separate schedule entries. The Member asserted that protirelin and thyrotropin-releasing factor are simply synonyms.

The Committee agreed to use the INN and cross-referencing the alternative name.

Viprinium

An entry already appears in Schedule 4 [viprynium]. It is a quaternary ammonium compound and it was asserted that it should be replaced by an amended entry for viprinium salts.

- XXXX DAP comment – all agreed with the proposal.

The Committee noted that the current Schedule 4 entry "viprynium", is currently harmonised with New Zealand. The spelling viprinium (i instead of y) appears to have been inadvertently introduced into the harmonisation table at the June 2006 NDPSC Meeting.

The Committee noted that while viprynium is used in New Zealand and in the SUSDP, this is actually a synonym of the INN and BAN pyrvinium. Members therefore agreed to vary the October 2006 decision so as to change to the INN spelling, and to include a cross reference for viprynium in the SUSDP index.

Vitamin D

The proposed amendment deletes the word "internal" before "therapeutic use". This extends coverage of the entry to products for external [*human therapeutic*] use (products for external use do not usually have a recommended daily dose (RDD) so would become Schedule 4). For example, a cream or ointment containing cod liver oil would be a restricted substance.

- XXXX DAP comment – The removal of the word "internal" was deliberate to harmonise with NZ.

Members noted Secretariat advice that a search of the ARTG located the following: 1 non-internal product containing ergocalciferol and 9 non-internal products containing cholecalciferol. Not all of these fall below the 0.01 mg/g general exemption from the requirements of scheduling. It was also likely that some of these creams/lotions would not have a RDD and would therefore go from unscheduled to Schedule 4. Members therefore agreed to set aside the October 2006 decision, and to instead recommend that New Zealand consider adopting the current limitation to the Schedule 4 entry for internal human therapeutic use only.

In addition the XXXX DAP Members identified a number of other editorial corrections which were addressed under item 21.1.1.

OUTCOMES

Quaternary Ammonium Compounds

The Committee confirmed that it was the intent of decision 2006/48-1 to schedule the parent compound rather than the salt with regard to quaternary ammonium compounds.

Potassium Chloride

The Committee agreed to:

- Confirm decision 2006/48-14 to amend the Schedule 4 entry for potassium chloride to include exemptions for preparations used in oral rehydration therapy, oral bowel cleansing prior to diagnostic medical and surgical procedures, enteral feeding an a general exemption cut-off of < 600 mg potassium chloride per dosage unit.
- Foreshadow consideration at the June 2007 NDPSC Meeting of a reduction in the general cut-off for the Schedule 4 potassium chloride entry.

Rifamycin

The Committee confirmed that part of decision 2006/48-1 amending the Schedule 4 rifampicin entry and creating a new Schedule 4 rifamycin entry.

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Quaternary Ammonium Compounds

The Committee agreed to vary decision 2006/48-1 (that part regarding an amendment to reword the Schedule 4 vecuronium bromide entry to “vercuronium”) to remove the extra r.

Schedule 4 – Amendment (Variation of Decision 2006/48-1)

VECURONIUM BROMIDE – amend entry to read:

VECURONIUM.

Alendronic Acid

The Committee agreed to vary decision 2006/48-1 (that part replacing the Schedule 4 alendronate sodium entry with an alendronic acid parent entry) as it was noted that there was already a Schedule 4 entry for alendronic acid. Members therefore agreed to delete the Schedule 4 alendronate sodium entry.

Schedule 4 – Amendment (Variation of Decision 2006/48-1)

ALENDRONATE SODIUM – delete entry.

Cobalt

The Committee agreed to vary decision 2006/48-1 (that part regarding a new Schedule 4 cobalt entry capturing therapeutic use) by:

- limiting the new Schedule 4 cobalt entry to human therapeutic use; and
- including an explicit exemption for "dicobalt edetate in preparations for the treatment of cyanide poisoning" in the new entry for consistency with the current Schedule 4 edetic acid entry.

Schedule 4 – New entry (Variation of Decision 2006/48-1)

COBALT for human therapeutic use **except** as dicobalt edetate in preparations for the treatment of cyanide poisoning.

Ethylhexanediol

The Committee agreed:

- that the new Schedule 4 ethylhexanediol entry (part of decision 2006/48-1) was intended to capture animal therapeutic use only, and confirmed the existing Appendix C entry for ethylhexanediol; and
- to vary decision 2006/48-1 (regarding ethylhexanediol) to correct the inadvertent omission of the † used to indicate that there was an Appendix C entry for ethyl hexanediol.

Schedule 4 – New entry (Variation of Decision 2006/48-1)

† ETHYLHEXANEDIOL.

Hexoprenaline

The Committee agreed to set-aside that part of decision 2006/48-1 regarding a new Schedule 4 hexoprenaline entry because an existing Schedule 4 hexoprenaline entry was inadvertently overlooked when the October 2006 NDPSC Meeting made the decision.

Nicotinic Acid

The Committee agreed:

- That the intension of the October 2006 NDPSC Meeting was to:
  - Amend the Schedule 3 nicotinic acid entry to capture preparations for human therapeutic use containing between 100 and 250 mg of nicotinic acid, exempting nicotinamide; and
  - Include a new nicotinic acid parent entry in Schedule 4 for human therapeutic use, except when captured by Schedule 3 or explicitly excluded from Schedule 3 (this last exemption was inadvertently omitted from decision 2006/48-16).
- To vary decision 2006/48-16 to:
  - Reflect the Schedule 3 exemptions in the new Schedule 4 nicotinic acid entry; and
  - Correct a minor editorial issue with the exemption numbering in the Schedule 3 nicotinic acid amendment.

Schedule 3 – Amendment (Variation of Decision 2006/48-16)

NICOTINIC ACID – amend entry to read:

NICOTINIC ACID for human therapeutic use in dosage preparations containing 250 mg or less of nicotinic acid **except**:

(a) in preparations containing 100 mg or less of nicotinic acid per dosage unit; or

(b) nicotinamide.

Schedule 4 – New entry (Variation of Decision 2006/48-16)

NICOTINIC ACID for human therapeutic use **except**:

(a) when included in other Schedules;

(b) in preparations containing 100 mg or less of nicotinic acid per dosage unit; or

(c) nicotinamide.

Thyrotropin-Releasing Factor

The Committee agreed:

- that decision 2006/48-1 (regarding separate entries for thyrotropin-releasing factor and protirelin) was an unnecessary duplication and that the new entry for thyrotropin-releasing factor should be set-aside;
- that inclusion of thyrotropin-releasing factor in brackets after the current protirelin entry should be removed for clarity as an editorial amendment in SUSDP 21 Amendment 3; and
- to include a cross reference for thyrotropin-releasing factor to protirelin in the index.

Schedule 4 – Amendment

PROTIRELIN – amend entry to read:

PROTIRELIN.

INDEX for SUSDP 22 Consolidation – New entry

Cross reference thyrotropin-releasing factor to protirelin.

Viprynium (Pyrvinium)

The Committee agreed:

- that the existing Schedule 4 viprynium entry was inadvertently overlooked due to a misspelling when the Committee made decision 2006/48-1 (that part including a new entry in Schedule 4 for viprinium);
- to vary that part of decision 2006/48-1 regarding viprinium to an amendment of the existing viprynium entry to reflect the INN spelling pyrvinium; and
- to include a cross reference for viprynium to pyrvinium in the SUSDP index.

Schedule 4 – Amendment (Variation of Decision 2006/48-1 to replace the Schedule 4 viprinium new entry in this decision)

VIPRYNIUM – amend entry to read:

PYRVINIUM.

INDEX for SUSDP 22 Consolidation – New entry

Cross reference viprynium to pyrvinium.

Vitamin D

The Committee agreed:

- that the October 2006 decision (part of 2006/48-1) to broaden the Schedule 4 vitamin D entry from internal use to all human therapeutic use would inadvertently capture those non-internal products which contain vitamin D at low levels but do not have a recommended daily dose required to qualify for the cut-off;
- to set-aside that part of decision 2006/48-1 regarding an amendment to the Schedule 4 vitamin D entry; and
- to recommend that New Zealand consider harmonising with the existing Schedule 4 vitamin D entry i.e. limit the entry to internal human therapeutic use.

2. PROPOSED CHANGES/ADDITIONS TO PARTS 1, 2, 3 AND 5 OF THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

2.1 SUSDP, PART 1

2.1.1 INTERPRETATION OF AEROSOL CONCENTRATION IN THE SUSDP

PURPOSE

The Committee considered the SUSDP interpretation of % with regard to pressurised spray aerosols, and whether to clarify the requirements for the statement of the quantity, proportion or strength of a poison contained in a pressurised spray aerosol.

BACKGROUND

The Secretariat was unable to locate any previous consideration of the interpretation of % with regard to aerosols.

DISCUSSION

A Member advised that there appeared to be some ambiguity in interpreting what was meant by % in schedule entries when applying this to pressurised aerosol preparations. Specifically, the Member noted the following.

- Paragraph 1.(3)(b) said that "one per cent" means "1 gram per 100 millilitres" for liquid preparations and "1 gram per 100 grams" for solid preps, but that this did not readily apply to aerosols which are liquid in a can.
- The Member noted that if the proportion of poison was calculated as wt/vol, then the manufacturer could simply make the volume of the can bigger so the liquefied propellant expands to a bigger volume, resulting in a lower % wt/vol of the poison in the product, possibly descheduling it.
- The Member suggested that it would be more sensible to calculate % for these preparations as % wt/wt. The Member therefore proposed that in paragraph 1.(3)(b)(ii) "solid or semi-solid" be replaced with "solid, semi-solid, or pressurised spray aerosol".
- The Member also advised that the NSW Trade Measurement Regulation 2002 requires pre-packaged "aerosol products" (other than therapeutic goods) to be clearly marked with their measurement by mass (only) when packed or sold.

The Committee was advised that another Member, while supporting the above recommendation, noted that, given that the NSW legislation has an exemption for therapeutic goods, would the TGA have any objections. The Members noted advice that *Therapeutic Goods Order 69* (TGO 69) “General requirements for labels for medicines” requires a specific weight, or weight range, rather than %. The *Required Advisory Statements for Medicine Labels* (RASML) directly adopts the current SUSDP paragraph 1.(3). XXXX confirmed that wt/actuation was used rather than % and therefore there should be no conflict between the above proposal and TGA’s requirements.

Members also noted that Part 2, paragraph 8.(2) requires that the statement of the quantity, proportion or strength of a poison, other than for human therapeutic use, must be expressed in the most appropriate of a number of forms including:

- if the poison is a liquid in a liquid preparation, as the mass or volume of the poison per stated volume of the preparation;
- if the poison is a solid or semi-solid in a liquid preparation, as the mass of the poison per stated volume of the preparation;
- if the poison is a gas in a liquid preparation, as the mass of the poison per stated volume of the preparation;

- if the poison is a gas in a gaseous preparation, as the mass of the poison per stated mass of the preparation.

The Committee noted that while adoption of the above proposal would mean % was to be measured as wt/wt (unless specified in the entry), the packaging requirements may allow % on the label to be expressed in an alternative form e.g. vol/vol or wt/vol if the scheduled substance is a liquid, solid or semi-solid, and the contents of the aerosol are liquid under pressure. Members therefore considered options which reflected the NSW Trade Measurement Regulation 2002's requirement.

The XXXX Member also advised of a review of 20 agvet aerosol products which assessed the regulatory impact of clarifying the % labelling requirement for aerosols. This review found that all but one of the products used wt/wt.

An XXXX pre-meeting comment noted the proposal and asserted that while confirmation of the definition with regard to aerosols was useful, it was not yet clear to XXXX whether or not there are specific labelling ramifications that may impact upon Trade Measurement legislation or upon international trade where wt/vol may be the regulatory standard expression.

Members generally agreed that amendments to paragraphs 1.(3)(b) and 8.(2) would address both the interpretation of % for aerosols in schedule entries; and clarify that the labelling requirements should match this interpretation i.e. % means wt/wt. However, it was noted that a possible change to paragraph 8.(2) was not included in the February 2007 pre-meeting gazette notice. Additionally it was noted that there was potential for wide regulatory impact on aerosol products, particularly those for domestic use. The Committee therefore agreed to foreshadow a decision for consideration at the June 2007 NDPSC Meeting to allow further stakeholder consultation.

OUTCOME

Due to potential for a large regulatory impact, particularly with regards to possible changes to labelling, the Committee agreed to foreshadow:

- an amendment to Part 1 Paragraph 1.(3)(b)(ii) to clarify that reference to "per cent" in a schedule entry for a pressurised spray aerosol means % weight in weight; and
- an amendment to Part 2 Paragraph 8.(2) (by adding a new part (a)) to clarify that the most appropriate form for labelling the strength, proportion or concentration for a pressurised spray aerosol is mass of the poisons per stated mass of the preparation.

FORESHADOWED DECISION (for consideration at the June 2007 Meeting).

Part 1 – Interpretation –Amendment

Paragraph 1.(3) – Amend entry to read:

(3) Unless the contrary intention appears where a concentration, strength or quantity is specified in a schedule or an appendix to this Standard in respect of a substance:

(a) if the substance is present as a salt, active principle or derivative (including an ester or ether), the concentration, strength or quantity is calculated as the equivalent amount of the substance that is listed in the Schedule or Appendix; and

(b) the expression "one per cent" means:

(i) in the case of a liquid preparation, 1 gram of the substance per 100 millilitres of the preparation; or

(ii) in the case of a solid, semi-solid or pressurised spray aerosol preparation, 1 gram of the substance per 100 grams of the preparation; and

(iii) any expression of greater or lesser percentages shall have a corresponding meaning; and

(c) in the case of codeine such concentration, strength or quantity is calculated as anhydrous codeine.

Part 2 – Labels and Containers – Amendment

Paragraph 8.(2) – Amend entry to read:

(2) if the poison is for a purpose or purposes other than human therapeutic use and:

(a) if the poison is in a pressurised spray aerosol preparation, as the mass of the poison per stated mass of the preparation;

(b) if the poison is a liquid in a liquid preparation, as the mass or volume of the poison per stated volume of the preparation;

(c) if the poison is a liquid in a solid or semi-solid preparation, as the mass or volume of the poison per stated mass of the preparation;

(d) if the poison is a solid or semi-solid in a liquid preparation, as the mass of the poison per stated volume of the preparation;

(e) if the poison is a solid or semi-solid in a solid or semi-solid preparation, as the mass of the poison per stated mass of the preparation;

(f) if the poison is a gas in a liquid preparation, as the mass of the poison per stated volume of the preparation;

(g) if the poison is a gas in a solid or semi-solid preparation, as the mass of the poison per stated mass of the preparation;

(h) if the poison is a gas in a gaseous preparation, as the mass of the poison per stated mass of the preparation;

2.2 SUSDP, PART 2

Nil items considered.

2.3 SUSDP, PART 3

2.3.1 [ITEM DELETED]

2.3.2 STORAGE STATEMENTS FOR SCHEDULE 2

PURPOSE

The Committee considered post-meeting comment regarding the October 2006 NDPSC Decision (2006/48-2) to amend Part 3, Paragraph 43 (the Schedule 2 storage statement).

BACKGROUND

Prior to decision 2006/48-2 the SUSDP recommended that States and Territories mandate the storage of poisons in Schedule 2, 3, 4 and 7 under Part 3, paragraphs 43 and 44:

43. A person who sells or supplies Schedule 2 poisons must keep those poisons in such a way that public access is restricted.

44. A person who sells or supplies Schedule 3, Schedule 4 or Schedule 7 poisons must keep those poisons in a part of the premises to which the public does not have access.

The June 2005 NDPSC Meeting noted that interpretation of paragraph 43 and 44 varied between jurisdictions and agreed that these paragraphs may not reflect the contemporary situation. Members agreed to refer this matter to NCCTG for policy consideration.

The October 2006 NDPSC Meeting considered NCCTG's response, and agreed to NCCTG's recommendation to amend Paragraph 43 to read "A person who sells or supplies Schedule 2 poisons must keep those poisons in such a way that public access to advice from a pharmacist is available if required". The Committee also agreed to defer any consideration of Paragraph 44 until the matter had been considered by NCCTG.

DISCUSSION

Members noted that a late post-meeting comment was received XXXX recommending that the Committee reconsider decision 2006/48-2 to amend Paragraph 43. XXXX recommended that the existing paragraph be retained or adapted to ensure consistency with both current State and Territory legislative requirements and Professional Pharmacy Standards and Guidelines with respect to storage of Schedule 2 poisons. This submission was received after the deadline for post-meeting comment. The Committee agreed, however, to use its discretion and consider this comment in this particular instance. Members confirmed that this was not setting a precedent for dealing with late comments in future.

Members particularly noted the following from the XXXX comment.

- The May 2006 NCCTG Meeting agreed that the SUSDP should be amended to reflect the general requirements for the availability of Schedule 2 medicines, noting "the current differing interpretations of paragraphs 43 and 44 did not support national uniformity".
- The October 2006 NDPSC Meeting noted "that this paragraph (43) did not restrict States or Territories from applying more stringent controls on pharmacies (and indeed was advised by a number of Jurisdictional Members that they would not be relaxing their current more restrictive access controls)."

<u>Lack of National Uniformity:</u>

- XXXX contended that decision 2006/48-2 did not support NCCTG's intention that the SUSDP should support national uniformity.
- The proposed amendment did not address the core issues – there was a requirement for a greater level of control within the jurisdictions and these levels of control were not uniform. In fact, it appeared that the Committee was advising individual jurisdictions to set their own controls on these matters and some jurisdictions have

indicated they intended to continue to do so. However, the variation between the jurisdictions was quite substantial. XXXX asserted that this was inconsistent with the ANZTPA principle, moving forward to the SUSMP, of adoption by reference.

- It appeared that the reason some individual jurisdictions advised that they will continue further regulation on this issue was because they recognised the importance of maintaining some control of the storage of Schedule 2 medicines and acknowledge that the national reference was inadequate in providing nationally consistent controls.
- XXXX asserted that implementation of a strong national reference to the storage and supply of scheduled medicines would give the individual jurisdictions the confidence to reference such standards without the need to implement additional controls.

Professional Duty of Care:

- XXXX reiterated the arguments presented at the October 2006 NDPSC Meeting that legislation should support the pharmacist to provide professional oversight of schedule medicines in line with their professional obligations. XXXX also reiterated the argument that the decision 2006/48-2 did not address the Galbally Review conclusions.
- XXXX contended that merely restricting scheduled medicines to sale from a pharmacy did not offer the same level of consumer support to ensure safe and effective use as would restricting the location for storage of medicines within a pharmacy.

The need to account for Pharmacy Practice:

- XXXX suggested current community pharmacy practice should also be considered. It was noted that it was becoming common for pharmacies to be in larger premises, and hence more departmentalised. Pharmacies of this type were likely to group Schedule 2 and exempt from scheduling medicines within product or disease categories.
- XXXX contended that the national legislation needs to consider current pharmacy practice and provide for "best practice" standards, not the lowest common denominator. As mentioned earlier in the Galbally reference, "the failure of even a few pharmacists to comply with such (professional) standards would pose an unacceptable level of risk."
- XXXX reiterated its October 2006 "promotional bins" argument, and the conclusion that should Schedule 2 medicines be permitted to be stored outside the professional services area of pharmacies, the sales interaction may not be with a staff member with any training in the sale of scheduled medicines, so the opportunity for the consumer to seek or receive professional advice is minimalised.
- For privacy reasons alone, the cash register was not an appropriate location for pharmacy staff to offer to assist the consumer to ensure that they have selected the right medicine for their needs and know how to use it optimally.

- This model of supply also assumed that the consumer would always make the correct choice of medicine or recognise when they required "access to advice from a pharmacist". XXXX repeated its arguments regarding consumers' ability to self-diagnose, do not recognise their misdiagnosis and the need for advice if they are taking other medications.

Future Scheduling Considerations:

- XXXX was concerned that decision 2006/48-2, by endorsing non-uniform jurisdictional controls instead of a strong national standard, could mean that future Committees may consider there was insufficient safety controls to allow for safe and effective down-scheduling.

Conclusion

- XXXX considers it imperative that for such matters as the storage of scheduled medicines, that Australia has a uniform, national regulation to ensure the supply of medicines was conducted professionally and responsibly and the public interest was protected. A suggested amendment would be:

43. A person who sells or supplies Schedule 2 poisons must keep those poisons in the designated professional services area of a pharmacy such that public access to advice from a pharmacist is available if required.

Members recalled the following from the October 2006 NDPSC Meeting.

- The May 2006 NCCTG Meeting agreed that the SUSDP should be amended to reflect the general requirements for the availability of Schedule 2 medicines, noting that there should be a graduated set of storage controls in place for medicines available only from the pharmacy based on unrestricted access (open shelf), behind the counter access by pharmacy staff only and the dispensary.
- Pre-meeting comments included the following points.
  - XXXX did not support the proposed amendment to paragraph 43 because:
    - the new wording could be interpreted as being less restrictive;
    - it could potentially allow unrestricted access to all Schedule 2 products within a pharmacy;
    - it would not necessarily enhance patient safety or promote quality use of medicines. XXXX asserted that while self-selection was an important element of OTC medicines, pharmacists also regularly encountered consumers who were unaware of the potential for harm with Schedule 2 (and similar) products and when and why they should seek advice;ty
    - through the different applications by States/Territories, the lack of consistency and uniformity across Australia will not be resolved;
  - XXXX did not support the proposed amendment to paragraph 43, asserting that:

- it would further weaken the regulatory framework for medicines in Australia;
- it may allow greater public access within licensed person premises such as country stores which have no access to a pharmacist;
- lack of storage restrictions would promote self-selection and the likelihood of the person checking with the pharmacist (or trained staff member) would decrease, increasing the likelihood of inappropriate medicine use;
- it was important that there were storage restrictions for Schedule 2 medicines to support the pharmacist's oversight of requests and to allow intervention and/or counselling as required. The safety profile of Pharmacy Medicines was such that they require pharmacist supervision;
- it was imperative that the SUSDP impose some restriction to allow regulatory authorities to ensure that the supply of medicines was conducted professionally and responsibly and the public interest was protected. XXXX recommended that the restrictions outlined in the current Paragraph 43 be retained or adapted to ensure consistency with current State and Territory legislative requirements with respect to storage of Schedule 2 poisons.

  - XXXX supported the proposed amendment as a sensible and practical change that more accurately reflected the appropriate storage conditions of Schedule 2 Poisons.
  - XXXX also supported the proposed amendment as providing greater clarity while also creating what XXXX asserted was the necessary and appropriate distinction between Schedule 2 and Schedule 3 poisons.

- The XXXX advised that current professional practice was about restricting Schedule 2 access to promote consumers seeking pharmacist advice, and that the apparent relaxation of controls could send a message counter to that of the professional bodies' QUM. In response, a Member noted that while NCCTG's recommended paragraph may seem to be a relaxation of controls for some jurisdictions, there was nothing to stop individual pharmacies applying additional controls as may be dictated by professional practice.
- A Member also asserted that the whole point of there being a Schedule 2 category was to control access by requiring these medicines to only be available in a pharmacy, not to control where in a pharmacy they had to be stored or sold. The Member noted that the original intent was to differentiate Schedule 2 from Schedule 3, in that Schedule 2 products could be self-selected and that if the consumer wished to seek advice then a pharmacist's advice would be available.
- A Member noted that the wording did not reflect the current practice of Schedule 2 licenses in which Schedule 2 products were supplied by non-pharmacies using State or Territory licensing – e.g. remote rural shops, optometrists, nurse practitioners, midwives, podiatrists, physiotherapists etc. The proposed wording mandated that "advice from a pharmacist is available if required", a requirement that was not

appropriate for many of these non-pharmacy suppliers. The existing paragraph 43 did apply to these alternative suppliers as the mandatory requirement was "public access is restricted". A Member asserted that a similar difference between the new and existing paragraph appeared to also apply to supply by doctors and to wholesalers of Schedule 2 products.

- The Committee agreed that the proposed new paragraph 43 should only be read in reference to supply and sale in a pharmacy setting. The non-pharmacist supply and/or sale would remain a matter for individual State or Territory licensing. The Committee also noted that this paragraph did not restrict States or Territories from applying more stringent controls on pharmacies.
- Another Member agreed that harmonisation at this basic level was a necessary first step to any longer term moves towards national consistency.
- Another Member suggested that the proposed paragraph should perhaps have started with "A pharmacist…" instead of "A person…". The Committee noted, however, that this probably would not cover a pharmacist's assistant or any other pharmacy employee who would normally be involved in the sale of Schedule 2 products. Indeed, if "A pharmacist…", a strict reading of the paragraph could imply that a pharmacist would need to directly make each and every sale of a Schedule 2 product. The Members agreed that "A person…" remained the appropriate start to the proposed paragraph.

A Member advised that one reason that the NCCTG decided to recommend a change to paragraph 43 was that some jurisdictions were using the "public access is restricted" part of the old paragraph to justify not having Schedule 2 products available for self-selection. The NCCTG wished to make it clear that paragraph 43 was not to empower such an interpretation, and that such additional controls would clearly be set solely at the discretion of jurisdictions. A Member suggested that perhaps NCCTG had sought to provoke a debate on the unharmonised nature of jurisdictional controls for Schedule 2 storage, but asserted that the NDPSC was not the appropriate place to have this debate.

The Committee generally agreed that the proposed NCCTG wording would allow all jurisdictions to continue with their current controls should they agree to adopt by reference (with some jurisdictions applying additional controls on top of this agreed minimum). Harmonisation efforts to improve the standard of practice to whatever is decided to be best practice was endorsed as a worthy undertaking, but one best pursued by a more appropriate fora.

OUTCOME

The Committee:

- noted that the post-meeting comment was received after the deadline;

- agreed, however, to use its discretion and consider this comment in this particular instance. Members confirmed that this was not setting a precedent for dealing with late comments in future; and
- confirmed the October 2006 NDPSC Decision (2006/48-2).

2.4 SUSDP, PART 5

2.4.1 APPENDIX A EXEMPTION FOR MEDICAL DEVICES

PURPOSE

The Committee considered the Appendix A exemption for medical devices.

BACKGROUND

In October 2002 the *Therapeutic Goods Amendment (Medical Devices) Act 2002* came into effect. The February 2003 NDPSC Meeting was advised that this new regime for medical devices adopted a classification system that had 5 classes of medical devices. The Meeting was also provided with a list of Class III ECRI medical devices which may require scheduling on the basis that they may contain scheduled substance(s) and were likely to be used outside the hospital or medical setting.

The June 2004 NDPSC Meeting agreed to foreshadow an Appendix A entry which exempted Class III medical devices containing scheduled substances. Members considered these devices to be of low abuse or misuse potential on the basis that they were used exclusively within the hospital or medical setting. In addition, it was also agreed that the Appendix A entry should specify those medical devices which are not appropriate for exemption. Members also agreed that the Committee be provided with future MDEC minutes to allow identification of medical devices which may be of interest to the Committee.

The October 2004 NDPSC Meeting agreed to the June 2004 foreshadowed decision to include the following entry in Appendix A to exempt Class III medical devices from the requirements of scheduling (with specified exclusions):

> MEDICAL DEVICES classified as Class III by the classification rules set out in Schedule 2 to the Therapeutic Goods (Medical Devices) Regulation 2002, as in force from time to time, **except**:
>
> (a) injectable tissue reconstructive, augmentation and restoration materials, including collagen;
>
> (b) medical devices which include anticoagulants;
>
> (c) artificial tears;

(d) urinary catheters; or

(e) intra-articular fluids.

DISCUSSION

The issue of the general exemption in Appendix A for Class III medical devices was discussed by the November 2006 NCCTG Meeting. The NCCTG noted that General Exemptions in the draft SUSMP reflected those listed in the current SUSDP [Appendix A]. Referring to the current exemption for particular medical devices, and current (*asserted*) variable application of this exemption by the states and territories, the NCCTG requested that the Committee review the intent and wording of this exemption.

Members noted advice from XXXX including the following.

- XXXX noted that the general exemption was put in place after consideration of the situation with medical devices that may contain a scheduled medicinal substance, in order to achieve meaningful public health outcomes in terms of labelling and controls over access and availability. It was drafted in the context that under the classification rules for medical devices, medical devices containing a medicinal substance are Class III. These were the devices most likely to contain a scheduled medicinal substance. The exceptions to this exemption were for devices that may be supplied to the public outside a hospital setting i.e. devices for which compliance with the SUSDP was appropriate.
- At the time, it was considered that other devices that may contain a substance scheduled in accordance with the SUSDP and were not Class III, by virtue of containing a medicinal substance, would in most instances be supplied to the public or used outside a hospital setting and therefore compliance with the SUSDP was appropriate. This would include disinfectants used on medical instruments.
- Subsequent experience identified at least one device, a dental adhesive, which contained a scheduled substance and was not Class III, but was appropriately exempted in accordance with the general exemption for medical and veterinary adhesives, glues and cements. XXXX has expressed concerns to the XXXX over the requirements for dental restorative materials to comply with the SUSDP.
- In drafting the exemption for Class III medical devices, XXXX noted that the Committee considered a list generated from the ARTG of devices that were likely to contain a medicinal substance. XXXX observed that this list may not have picked up devices that contained a scheduled substance that was not a medicine.
- XXXX believed that the current wording of the exemption in Appendix A remained relevant for devices containing a medical substance. However, XXXX also asserted that it would be appropriate to consider a general exemption for devices containing a scheduled substance other than a medicine, with some exceptions. If the Committee

considered this to be feasible, the XXXX indicated that it would work to develop the list of possible exceptions to the general exemption.

Member's also noted the following from TGA's current Australian Medical Devices Guidelines (http://www.tga.gov.au/docs/html/devguid1.htm), and Medical Devices Classification Guidelines (http://www.tga.gov.au/docs/html/devguid25.htm).

- A medical device is defined in the legislation as "any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended by the person under whose name it is to be supplied, to be used for human beings for the purposes of one or more of the following:
  - diagnosis, prevention, monitoring, treatment or alleviation of disease,
  - diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
  - investigation, replacement or modification of the anatomy or of a physiological process,
  - control of conception,
  - and does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means; or an accessory to such an instrument, apparatus, appliance, material or other article." (an accessory, to a medical device, is an article, or articles intended specifically by its manufacturer to be used together with the medical device to enable the medical device to be used as intended by its manufacturer).
- The five classes of medical device are:
  - Class I – for low risk medical devices (includes low risk devices that are sterile and/or have a measuring function)
  - Class IIa – for low-medium risk medical devices
  - Class IIb – for medium-high risk medical devices
  - Class III – for high risk medical devices
  - AIMD – for Active Implantable Medical Devices (treated as Class III medical devices)

Pre-meeting comments were received from XXXX and XXXX noting an interest in this item.

The November 2006 NCCTG Meeting also requested advice from the Committee regarding the intent and application of the general exemption in Appendix A for medical devices in Australian states and territories and New Zealand. The following points were noted.

- Queensland adopts the Appendix A exemptions under the Health (Drugs and Poisons) Regulation 1996, so Class III medical devices specified in the Appendix A entry are exempted from scheduling and all associated controls in Queensland.
- Tasmania adopts Appendix A by reference and therefore it is effective as a Tasmanian Regulation.
- The Victorian *Drugs, Poisons and Controlled Substances Act 1981* adopts by reference Schedule 2-9, including Part 1Interpretation, which in paragraph (2)(g) states that a schedule does not include a preparation or product included in Appendix A. Consequently, Victorian legislation is consistent in the application of exclusions and exemptions with respect to medical devices and Appendix A.
- Appendix A is adopted by reference under the South Australian *Controlled Substances Act 1984*. So the exceptions and exemptions with respect to medical devices detailed in Appendix A apply in South Australia.
- Appendix A of the SUSDP is adopted by reference in the NT *Poisons and Dangerous Drugs Act*. Therefore the general exemption for Class III medical devices applies in the NT.
- WA adopts Appendix A in the Poisons Regulations 1965. Regulation 2A states that the provisions of the Poisons Act and its Regulations do not apply to poisons listed in a product listed in Appendix A of the SUSDP.
- Each Schedule of the NSW Poisons List exempts by reference any product listed or described in Appendix A of the SUSDP.
- New Zealand does not have device registration and so all devices are exempt from scheduling as they are not classed as medicines.

Members agreed that the current Appendix A entry remained appropriate but expressed some concern that XXXX may not be requiring non-exempt medical devices to comply with all controls if they contain a scheduled, but not human therapeutic, poison. Members requested that XXXX work to develop the list of possible exceptions to their proposed general exemption for devices containing a scheduled substance other than a medicine. Consideration of such a proposal would not be appropriate until such a list was available.

OUTCOME

The Committee confirmed:

- the current Appendix A entry exempting class III medical devices containing Scheduled substances as these have low abuse or misuse potential as they are used exclusively within hospital or medical settings; and
- the current exclusions from this exemption for those specific devices identified as having a use pattern which may include use outside a hospital setting.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

3. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCY)

Nil items considered.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 METHYL METHACRYLATE AND ETHYL METHACRYLATE

PURPOSE

The Committee considered scheduling of methyl methacrylate (MMA) and ethyl methacrylate (EMA), including a foreshadowed MMA decision and post-meeting comment on the October 2006 NDPSC decisions (2006/48-10) regarding MMA and EMA for cosmetic use.

BACKGROUND

MMA is a clear liquid with a distinctive, sharp, fruity odour. MMA is widely used because single molecules of MMA monomer link together to form a very strong, hard polymer that bonds tightly to a variety of substances. The principal application of MMA is the production of polymethylmethacrylate acrylic plastics. MMA is also used for the production of the co-polymer methyl methacrylate-butadiene-styrene, used as modifiers for PVC. MMA polymers and co-polymers are also used for waterborne coatings, such as latex house paint.

MMA has also been used in cosmetic nail products, but following concerns about sensitivity and fingernail damage arising from the strength of the MMA nail coating, several countries have imposed restrictions and/or bans to the use of MMA in nail products.

EMA, a clear liquid, is a base material for coatings and adhesives. It is used in resins, solvent, oil additives, dental products, textile emulsions, leather and paper finishing. Additionally, as a result of international limits to the use of MMA in cosmetic nail preparations, EMA has been used as a substitute for MMA and is promoted as a safer alternative. These EMA nail products are sold as two part formulations with EMA being cross linked with methacrylates to form the finished nail.

At the May 1974 DPSSC Meeting several dozen compounds were exempted from scheduling without any clear rationale being recorded. This list included EMA. Appendix B was deleted from the SUSDP at the August 1995 NDPSC Meeting. The February 2003 Meeting agreed to reinstate Appendix B, including the EMA listing.

The October 2006 NDPSC Meeting noted advice from NICNAS regarding MMA and EMA. The Committee agreed, with regards to MMA, that the cosmetic use of MMA posed sufficient danger as to warrant prohibition of sale, supply and use through inclusion in Appendix C. The Members further agreed:

- that the severe dermal irritancy, moderate respiratory irritancy and evidence of moderate sensitising potential of MMA constituted a moderate potential for causing harm (when for non-cosmetic uses), the extent of which could be reduced through the use of appropriate packaging and labelling;
- that the risk from MMA relates to the monomer form only and not to polymers which include methyl methacrylate in chemically combined form; and
- to foreshadow Schedule 6 (excluding derivatives) and Appendix F entries for MMA.

With regards to EMA, the Committee agreed:

- that continued Appendix B listing of ethyl methacrylate was not justified given the irritancy and skin sensitisation risks;
- that the risk from EMA relates to the monomer form only and not to polymers which include ethyl methacrylate in chemically combined form;
- to create new Schedule 5 and Appendix F entries for EMA as the low irritancy and skin sensitisation risks could be managed through the use of appropriate packaging and labelling; and
- that no concentration exemption should apply, as EMA was a skin sensitiser even at low concentrations.

DISCUSSION

Members noted the following from XXXX pre-meeting/late post-meeting comment.

- XXXX requested consideration of the precise application when scheduling MMA and EMA monomers for cosmetic use so that other applications were not affected.
- XXXX advised that XXXX acrylic resins for use as nail varnish for global distribution, and asserted that the scheduling would disadvantage XXXX as trace amounts of monomer in the polymer would require the product to be scheduled (unless < 10 mg/kg), noting that the level of allowable residual EMA and MMA monomers was <1% in some other global jurisdictions.

- XXXX observed that the concern at the October 2006 NDPSC Meeting was adhesive applications i.e. polymerized in situ to adhere a false nail. These adhesives may theoretically have up to 100% free monomer but are expected to range from 40 to 85% free acrylic monomer depending on the type of product.
- However, XXXX advised that EMA and MMA monomers may also be used to manufacture acrylic polymers for high quality, lusterous, difficult to chip nail polish varnishes. Such varnishes may have total residual free monomer levels typically between 0.1 and 0.5% on resin solids. Nail polish products using polymers have been on the global market for a number of years without any problems being known.
- The October 2006 NDPSC Meeting concluded that since these monomers are sensitizers there was no safe level for a cut-off. However, the allowable concentration in the workplace under the ASSC Hazardous Substances Information System (HSIS), through its cut-off limit for sensitization (R43), was < 1%.
- XXXX therefore suggested alternative solutions specifically targeting the problem products and applications i.e. nail adhesives characterized by high levels of free MMA and EMA monomer (>1%).

Members also recalled the following from the NICNAS submission regarding cosmetic use of MMA considered at the October 2006 NDPSC Meeting.

- The FDA restricted the use of 100% monomer MMA in cosmetic nail products due to risk of sensitisation and fingernail damage by court action in 1970. In 2005, the FDA confirmed that MMA in cosmetic fingernail preparations was a "poisonous and deleterious substance" and approximately 30 US states have banned or recommended against the use of MMA in nail preparations. Health Canada imposed a ban in 2003 on all cosmetic nail products containing MMA on human health grounds. ERMA New Zealand has banned the use of MMA in cosmetic nail products through its Group Standard for Cosmetics.
- Reports indicated that, in addition to the direct toxicological concerns arising from use of MMA, concerns arose from the harder nature of the bonding layer when MMA rather than EMA was used. These include difficulty in removal, requiring mechanical grinding or, alternately, 2 hour soaking in acetone, and mechanical damage to the nail plate when impact occurs on the finished nail in use, due to lack of "give".

<u>Toxicity profile</u>

- Members noted that there was strong evidence of cross-reactivity between MMA and EMA for sensitisation and additive effects for respiratory irritation.
- Members also noted the following toxicity profiles provided by NICNAS for MMA.
  - Low acute oral toxicity (LD_{50}: dog - 4700 mg/kg bw, rat - 7552-9440 mg/kg bw).
  - Low acute dermal (LD_{50}: rat > 5000 mg/kg bw) and inhalation toxicity (LC_{50}: rat and mouse - 3750-7268 ppm, 4 hour).

- Severe dermal irritant. In humans, 5% MMA produced skin reactions in 18/20 volunteers. Mild eye irritant. Moderate respiratory irritant.
- Evidence of moderate sensitising potential.
- Low repeated dose toxicity.
- Not determined to be mutagenic or carcinogenic.
- Data indicated that MMA was not embryotoxic, foetotoxic or teratogenic.
- In addition to health hazards MMA can also cause damage to the nail bed from chemical and/or mechanical issues.

Exposure and Risk

- The most probable exposures related to inhalation of vapour and short term small volume skin contact in the immediate vicinity of the fingernail. Exposure was much more probable from home use than in salon use by trained personnel.
- The saturated vapour pressure was much higher than the concentrations at which respiratory irritation have been observed, and accordingly there was significant risk of respiratory irritation following use without efficient ventilation systems. The irritant response was likely to result in low risk of higher vapour exposures at concentrations giving rise to systemic effects.
- Short term small volume dermal exposure on a repeated basis was likely to result in a primary risk of skin sensitisation rather than dermal irritation.
- Accordingly, the risks of respiratory irritation and skin sensitisation were likely to be high under certain circumstances. The threshold for respiratory irritation was lower for MMA than for EMA, and the higher vapour pressure of MMA meant that the threshold concentration will be more rapidly attained in the absence of efficient ventilation. The results of animal testing indicate that MMA is a more potent skin sensitiser, at least in the induction phase, than EMA.

The October 2006 NDPSC Meeting also noted the following NICNAS recommendation regarding MMA (recommendations were for MMA in monomer form only, and did not apply to polymers which include MMA in chemically combined form).

- The NDPSC may consider it appropriate to include:
  - MMA (excluding its derivatives), for use in cosmetic preparations for fingernail use in Appendix C of the SUSDP;
  - MMA (excluding its derivatives) in Schedule 6 for other uses. No minimum concentration should apply, as MMA is thought to be capable of inducing sensitisation at even low concentrations.

Members also recalled the October 2006 NDPSC Meeting's consideration of the following from XXXX pre-meeting comment regarding MMA.

- Online industry advice regarding MMA for cosmetic nail use:
  - American Beauty Association, Nail Manufacturers Council - "The Nail Manufacturers Council wants you to be informed about the potential dangers related to the use of MMA. We agree with the FDA that the use of liquid nail enhancement products containing MMA is unsafe and unwise";
  - The Methacrylate Producers Association (MPA) - "MPA members have for many years recommended that methacrylic acid and its esters in their unreacted monomeric liquid form not be used in cosmetics."
- XXXX recommended that the Committee clearly distinguish the legitimate industrial uses of MMA, and that trace amounts of MMA that may be present in copolymers do not fall within the scope of any regulatory proposals for this substance. With regard to the latter, XXXX suggested that the provisions of Article 4.2 of the EU Cosmetics Directive should apply – to the effect of:
  "The presence of traces of the substances listed in Annex II shall be allowed provided that such presence is technically unavoidable in good manufacturing practice and that it conforms with Article 2 (Article 2 states that cosmetics should not be harmful to humans in the normal and reasonably foreseeable conditions of use etc)."

The Members agreed that the intent of decision 2006/48-10 for MMA – Appendix C for cosmetic use – and the foreshadowed Schedule 6/Appendix F entries, were appropriate. However, there was agreement that the practical limitations of manufacturing polymers i.e. a small amount of residual monomer is always present, meant that the current 10mg/kg limit may be unobtainable. Members considered the risks of ≤ 1% MMA monomer, when present as a residue in a polymer, were low enough to allow an exemption from scheduling. However, the Committee confirmed that this was only for residual monomer present from manufacture of a polymer, and that the cut-off would not apply to a product which had deliberately introduced MMA monomer.

At the February 2007 NDPSC Meeting the Members considered the issue of MMA, but inadvertently overlooked the EMA issue. However, following the February 2007 NDPSC Meeting a Member raised an issue regarding the decision (2006/48-10) to include a new entry in Schedule 5 for EMA "ETHYL METHACRYLATE (excluding its derivatives) for cosmetic use".

As the Member noted, this meant that residues of EMA in polymers for cosmetic use above 10 mg/kg would be required to comply with Schedule 5. The similar situation with MMA was resolved at the February 2007 NDPSC Meeting by adding "**except** in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer".

A proposal was therefore considered by the Committee out-of-session to vary decision 2006/48-10 (regarding EMA) to reflect the MMA exemption wording.

DECISION 2007/49 - 7

The Committee confirmed the intent of the October 2006 decision that:

- the cosmetic use of MMA posed sufficient danger as to warrant prohibition of sale, supply and use through inclusion in Appendix C; and
- the low irritancy and skin sensitisation risks of EMA could be appropriately reduced through including a new Schedule 5 entry for cosmetic use and to create an Appendix F entry providing appropriate warning statements and safety directions.

However, the Committee also:

- noted that the post-meeting comment (that part of the comment referring to MMA and EMA for cosmetic use) was received after the deadline;
- agreed to use its discretion and consider this comment in this particular instance. Members confirmed that this was not setting a precedent for dealing with late comments in future; and
- agreed to vary decision 2006/48-10 (the new EMA Schedule 5 entry, and MMA Appendix C entry, for cosmetic use) as the risks were sufficiently reduced when there was ≤ 1% monomer present as a residue in a polymer as to warrant exclusion from the requirements of scheduling.

The Committee also confirmed the foreshadowed decision:

- to include new entries in Schedule 6 and Appendix F for MMA as the severe dermal irritancy, moderate respiratory irritancy and evidence of moderate sensitising potential constituted a moderate potential for causing harm (when for non-cosmetic uses), the extent of which could be reduced through the use of appropriate packaging and labelling;
- that the risk from MMA related to the monomer form, not to polymers which included MMA in chemically combined form; and
- that the risks from MMA are sufficiently reduced when there is ≤ 1% monomer present as a residue in a polymer as to warrant exclusion from the requirements of scheduling.

Schedule 5 – New entry (Variation of Decision 2006/48-10)

ETHYL METHACRYLATE (excluding its derivatives) for cosmetic use **except** in preparations containing 1 per cent or less of ethyl methacrylate as residual monomer in a polymer.

Schedule 6 – New entry

† METHYL METHACRYLATE (excluding its derivatives) **except** in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer.

Appendix C – New entry (Variation of Decision 2006/48-10)

METHYL METHACRYLATE for cosmetic use **except** in preparations containing 1 per cent or less of methyl methacrylate as residual monomer in a polymer.

Appendix F – New entry

Poison	**Warning Statement**	**Safety Directions**
Methyl methacrylate	28	4,9,23

4.2 BASIC ORANGE 31

PURPOSE

The Committee considered scheduling of Basic Orange 31.

BACKGROUND

Basic Orange 31, a phenylenediamine azo linked to an imidazole, is used predominantly as a hair dye. The Chemical name of this substance is 2-[(4-aminophenyl)azo]-1,3-dimethyl-1H-Imidazolium chloride.

The October 2006 NDPSC Meeting agreed to:

- a Basic Orange 31 Schedule 6 entry as it was a severe eye irritant and a potential sensitiser;
- allow an exemption for hair dyes containing ≤ 1% Basic Orange 31, when appropriately labelled, as:
  - ≤ 1% Basic Orange 31 was not a skin irritant, only a slight eye irritant and the risk of local adverse effects was low; and
  - that the risk of sensitisation when in hair dyes, while low, could not be ruled out, but could be adequately addressed by appropriate labelling.
- foreshadow inclusion of Basic Orange 31 in Appendix C for skin colouration and dyeing of eyelashes or eyebrows because of potential sensitisation and the irritation risk to eyes.

DISCUSSION

Members recalled the following from the October 2006 NDPSC consideration of a NICNAS assessment of Basic Orange 31.

- Basic Orange 31 was intended for both oxidative and non-oxidative hair dye products for domestic and salon use. The concentration of Basic Orange 31 would be ≤ 0.5%.
- The following toxicological data was presented:

Endpoint	*Assessment Conclusion*
Rat, acute oral	harmful, LD_{50} = 1000 - 2000 mg/kg bw
Rat, acute dermal	low toxicity, LD_{50} > 2000 mg/kg bw
Rabbit, skin irritation (acute)	slightly irritating
Rabbit, skin irritation (repeat dose)	slightly irritating
Rabbit, eye irritation	severely irritating (100%) slightly irritating (1%)
Guinea pig, skin sensitisation (adjuvant test)	no evidence of sensitisation
Skin sensitisation – LLNA	evidence of sensitisation
Phototoxicity	does not exhibit a phototoxic potential
Photoallergenicity	does not exhibit a photoallergenic and allergenic potential
Rat, repeat dose oral toxicity (14 days)	NOEL 15.5 mg/kg bw/day
Rat, repeat dose oral toxicity (90 days)	NOAEL 63 mg/kg bw/day, NOEL 18 mg/kg bw/day
Genotoxicity (bacterial reverse mutation)	non mutagenic
Genotoxicity (*in vitro* chromosome aberration test chinese hamster cells)	clastogenic
Genotoxicity (*in vitro* chromosome aberration test human lymphocytes)	non clastogenic
Genotoxicity (*in vitro* cell gene mutation test)	non mutagenic
Genotoxicity (*in vivo* mouse micronucleus test)	non genotoxic
Genotoxicity (*in vivo* UDS test)	non genotoxic
Toxicokinetic studies	absorption 0.018+0.005 μg/cm2
Developmental and reproductive effects	maternal & foetal NOAEL 60 mg/kg bw/day

<u>Hazard</u>

- Based on the available data, NICNAS classified Basic Orange 31 as a hazardous substance. The classification and labelling details were:
  - R22 Harmful if swallowed
  - R41 Risk of serious damage to eyes
  - R43 May cause sensitisation by skin contact

Risk

- *Irritation and Sensitisation*
  - The public would be exposed at a maximum concentration of 0.2%, a concentration that was unlikely to be a skin irritant, was expected to only be a slight eye irritant and was below the EC3 value for sensitisation. Therefore the risk of local adverse effects was considered to be low, however, the risk of sensitisation could not be ruled out.
  - The highest amount of Basic Orange 31/unit area on the skin was calculated as 26 $\mu g/cm^2$ for the home-use product. Based on a worst-case EC-3 value of 0.9% a skin potency value for the notified chemical was calculated at 225 $\mu g/cm^2$. This gives a margin of safety of 8.6 for the estimated maximum dermal exposure. Although this is lower than the desired margin of safety of 100, Basic Orange 31 was considered to be a less potent sensitiser than p-phenylenediamine.
  - The product labelling advised that the product may cause an allergic reaction or cause skin irritation. A preliminary skin test was also advised which should identify individuals susceptible to sensitisation.
- *Systemic effects*
  - The highest public exposure to the notified chemical was estimated as 0.036 mg/kg bw/day (although due to expected low percutaneous absorption this is expected to be an overestimate). Based on the lowest NOEL of 15.5 mg/kg bw/day, derived from the 14-day rat oral study the lowest margin of exposure (MOE) was 435. MOE ≥ 100 was considered acceptable to account for intra- and inter-species differences. Therefore the risk of systemic effects from use of hair dyes containing the notified chemical was considered to be low.

Conclusion

- There was no significant concern to public health when used in the proposed manner and provided the hair dye formulations were adequately labelled to indicate sensitisation potential. NICNAS recommended that a number of safety directions be mandated on the label (the October 2006 NDPSC Meeting agreed to this recommendation and included a reverse schedule entry such that failure to apply the labels would move the product from unscheduled to Schedule 6).

Members also recall the following from the EU's Scientific Committee on Cosmetic Products and Non-food Products report on Basic Orange 31.

- Acute oral toxicity: LD_{50} > l000 mg/kg but < 2000 mg/kg. Acute dermal LD_{50} > 2000 mg/kg bw. Repeated dose oral toxicity suggested a NOAEL of 53 mg/kg bw/day. The sub-chronic oral toxicity yielded a NOEL of 18 mg/kg bw/day and an NOAEL of 60 mg/kg bw/day.

- Basic Orange 31 did not reveal any teratogenic effects. The NOAEL was set at 60 mg/kg bw/day for maternal and foetal effects. It was considered non mutagenic/genotoxic.
- The test material was considered to be slightly irritating to the skin. A 1% solution was slightly irritating to the eye. It was considered not to be a sensitiser. It induced delayed contact hypersensitivity in the murine Local Lymph Node Assay.
- Basic Orange 31 exhibited neither phototoxic nor photoallergic potential.
- A total of 0.009 % of the applied dose was reported to have penetrated, corresponding to a percutaneous absorption of 0.018 μg/cm². However, the substance was not tested in the presence of an oxidising agent. The applied dose of 101 mg/cm² was higher than the amount recommended by the SCCNFP (20 mg/cm²).
- The SCCNFP was of the opinion that Basic Orange 31 might be regarded as safe in general. However, the data was insufficient for a final evaluation.

The October 2006 NDPSC Meeting also noted a request from the SCCNFP to the EU's Scientific Committee on Consumer Products (SCCP) regarding:

- does the SCCP consider Basic Orange 31 to be safe for use in non-oxidative and oxidative hair dye formulations taken into account the scientific data provided?
- does the SCCP recommend any restrictions with regard to the use of Basic Orange 31 in non-oxidative and oxidative hair dyes formulations?

An October 2006 pre-meeting comment noted the above request to the SCCP and asserted that this report may assist to inform the Committee's considerations. It was therefore proposed that the Members defer consideration of this item until the SCCP report became available. Members agreed that it may be some time before the SCCP report was publicly released and that the Committee had sufficient data before it to allow consideration at this time. The Committee did agree to request that the SCCP report be tabled for the information of Members when it became available. [Members noted that no report appears to have been released to date].

The October 2006 NDPSC Meeting also foreshadowed consideration of whether the sensitisation and irritancy risks from Basic Orange 31 were such that it should be banned for certain use patterns. Members raised particular concerns about use on the skin, for applications such as tattoo inks, and use in eyelash or eyebrow tints.

An XXXX post-meeting comment was received proposing that the Committee consider a variation to the schedule entry for Basic Orange 31 set at the October 2006 NDPSC Meeting in line with the proposal on labelling requirements for single use composite pack hair preparations as discussed under item 8.2.

DECISION 2007/49 - 8

The Committee:

- confirmed decision 2006/48-11 to include an entry in Schedule 6 for Basic Orange 31 as it is a severe irritant to the eye and a potential sensitiser, with an exemption for hair dyes containing ≤ 1% basic orange 31, when appropriately labelled.
- agreed to include an entry in Appendix C for Basic Orange 31 when for skin colouration or dyeing of eyelashes and eyebrows as the severe eye irritant and sensitiser potential risks for these use patterns are of such danger to health as to warrant prohibition of sale, supply and use.
- agreed to editorially amend the Schedule 6 entry, once the Appendix C entry was implemented, to include the † symbol used to indicate that the entry had an Appendix C listing associated with it.

Schedule 6 – Amendment (Editorial change to coincide with the Appendix C entry)

BASIC ORANGE 31- Amend entry to read:

† BASIC ORANGE 31 (2-[(4-aminophenyl)azo]-1,3-dimethyl-1H-Imidazolium chloride)
except in hair dye preparations containing 1 per cent or less of Basic Orange 31 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN;

If in eyes wash out immediately with water; and

WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

Appendix C – New Entry

BASIC ORANGE 31 (2-[(4-aminophenyl)azo]-1,3-dimethyl-1H-Imidazolium chloride)
in preparations for skin colouration and dyeing of eyelashes or eyebrows.

4.3 SULFENTRAZONE

PURPOSE

The Committee considered the scheduling of sulfentrazone.

BACKGROUND

At the June 2006 NDPSC meeting, the Committee noted that XXXX had sought approval of a new active constituent, sulfentrazone. This new chemical was intended for use as a XXXX In providing an assessment of the toxicology in support of XXXX

The Committee agreed to include sulfentrazone in Schedule 7 of the SUSDP having regard to its toxicity and, in particular, its developmental and reproductive toxicity. This recommendation would have come into effect on 1 January 2007.

However, the Committee noted post-meeting correspondence which had been received from XXXX

XXXX

Prior to receiving the post-meeting correspondence from XXXX, the Secretariat had been approached with a request that the Committee's recommendation not be progressed. The Secretariat advised that the Committee's decision to place sulfentrazone in Schedule 7 could not be undone without further information and reconsideration by the Committee.

The applicant was informed that the SUSDP listed all substances, not just currently marketed substances and inclusion in the SUSDP was in no way any indication of a product being available. Also, should they wish to write to the Committee explaining that XXXX, this correspondence would be put to the Committee as a post (June 2006) meeting submission.

The Committee was requested to consider setting-aside its decision to include sulfentrazone in Schedule 7, noting that the applicant did not agree with the toxicological assessment and did not have the opportunity to comment on XXXX report prior to the June 2006 NDPSC Meeting .

The Committee received from XXXX, a detailed account of the events which XXXX contended had led to their inability to comment on the scheduling proposal put forward in XXXX toxicological assessment report prior to consideration by the NDPSC. As the Committee had seen data which had suggested XXXX the appropriateness of a Schedule 7 entry, it was appropriate that the scheduling recommendation remain. XXXX The Committee was mindful of the fact that confusing circumstances had surrounded the timing of the referral of XXXX toxicological assessment report to XXXX which had in turn impacted upon XXXX opportunity to comment on the report prior to consideration

of scheduling by NDPSC. The Committee therefore agreed to set aside its previous decision and to reconsider the matter at its February 2007 NDPSC Meeting.

Whilst the Committee was sympathetic to XXXX and the mitigating circumstances surrounding their submission, the Committee wished to make it clear that the decision in no way set a precedent for future sponsors. The Committee only set aside the decision of the June 2006 NDPSC Meeting (and would re-gazette for the February 2007 NDPSC Meeting) to ensure that due process was followed in this particular instance.

The Committee was advised by XXXX and XXXX that to avoid similar confusion to that which had arisen in this matter, XXXX and XXXX would in future amend correspondence to applicants to make it clear that scheduling and associated issues subsequent to the completion of XXXX assessment should be addressed directly with the NDPSC Secretariat and not XXXX or XXXX.

The Committee noted the post-meeting comments received from XXXX and agreed to set aside its previous decision. The Committee also agreed to foreshadow consideration of the inclusion of sulfentrazone in Schedule 7 at the February 2007 NDPSC Meeting.

DISCUSSION

Post-meeting comment was received from XXXX objection to the scheduling of sulfentrazone. XXXX Members considered this post-meeting comment out-of-session as it had been inadvertently omitted from the Meeting papers. The Committee agreed that the comment did not provide any new information relevant to the scheduling consideration of sulfentrazone.

DECISION 2007/49- 9

The Committee agreed to confirm the foreshadowed decision taken at the October 2006 meeting to include sulfentrazone in Schedule 7 of the SUSDP.

Schedule 7 – New entry

SULFENTRAZONE.

4.4 CLOTHIANIDIN

PURPOSE

The Committee considered the scheduling of clothianidin.

BACKGROUND

The Committee recalled that at the October 2006 meeting of the NDPSC, the Committee had received from XXXX an assessment of the toxicological data provided in support of the registration of XXXX containing the active ingredient, clothianidin.

The Committee noted that Clothianidin XXXX

On the basis of its high acute oral toxicity in mice, clothianidin had been (previously) included in Schedule 6 of the SUSDP. A cut-off was not established as the product considered at the time also had an acute toxicological profile consistent with inclusion in Schedule 6.

XXXX

XXXX suggested that the NDPSC may wish to consider it appropriate to include clothianidin in preparations containing 20 per cent or less of clothianidin in Schedule 5 of the SUSDP.

For the information of the NDPSC, XXXX also provided a copy of the Advisory Committee on Pesticides and Health (ACPH) discussion of clothianidin (October 2002). This consideration by ACPH had been requested by the NDPSC during its earlier consideration of clothianidin.

The Committee agreed to foreshadow that, based on the acute toxicity, clothianidin in preparations containing 20 per cent or less of clothianidin be included in Schedule 5 of the SUSDP. XXXX

DISCUSSION

The Committee was advised that XXXX had provided post-meeting comment on the Committee's decision to foreshadow a Schedule 5 entry for clothianidin in preparations containing 20 per cent or less and to the Committee's request XXXX

The company indicated that XXXX

A timeframe for submission of the study and for its evaluation by the OCS had been agreed between XXXX.

XXXX had therefore requested that further consideration of the scheduling of clothianidin be deferred until the June 2007 meeting.

OUTCOME

The Committee agreed to defer further consideration of the scheduling of clothianidin until the June 2007 NDPSC meeting.

4.5 GHRH INJECTABLE PLASMID

PURPOSE

The Committee considered the scheduling of GHRH Injectable Plasmid.

BACKGROUND

At its October 2006 meeting, the Committee was advised that XXXX.

It was noted that in mammals, GHRH is a 44-amino acid peptide hormone produced in the arcuate nucleus of the hypothalamus. GHRH is released from neurosecretory nerve terminals of arcuate neurons, and is carried by the hypothalamo-hypophysial portal circulation to the anterior pituitary gland where it stimulates GH secretion.

The actions of GHRH are opposed by another hypothalamic hormone, somatostatin, also known as growth hormone-inhibiting hormone (GHIH). Somatostatin is released from neurosecretory nerve terminals of periventricular somatostatin neurons, and is carried by the hypothalamo-hypophysial portal circulation to the anterior pituitary where it inhibits GH secretion by hyperpolarising the somatotropes (the cells in the anterior pituitary that secrete growth hormone). Somatostatin and GHRH are secreted in alternation, giving rise to the pulsatile secretion of GH. Growth hormone acts on tissues directly and also indirectly via the production in the liver in response to growth hormone of insulin-like growth factor I (IGF-I).

The somatostatin releasing neurons in the hypothalamus mediate negative feedback effects of growth hormone on its own release; the somatostatin neurons respond to high circulating concentrations of GH and IGF-I. Levels of the various hormones and factors are tightly controlled by each other in a natural “feedback loop”.

XXXX

Therefore, XXXX suggested that NDPSC could consider that the active, synthetic DNA expression cassette encoding for porcine growth hormone-releasing hormone (GHRH), should be placed in Appendix B of the SUSDP. On the other hand, noting that veterinarians are experienced in giving injections to animals, the NDPSC may consider limiting the potential for self-injection by placing it in Schedule 4.

XXXX and the XXXX confirmed that XXXX had been consulted and advised of this application during the course of the process assessment by both XXXX and XXXX. The advice from XXXX would be made available to the February 2007 NDPSC Meeting.

The Committee agreed to foreshadow that GHRH Injectable Plasmid be included in Schedule 4 of the SUSDP noting the need for veterinary supervision. The scheduling of GHRH would therefore again be considered at the February 2007 NDPSC Meeting.

DISCUSSION

The Committee was advised that no post-meeting submissions had been received in relation to the Committee's foreshadowed decision to include GHRH Injectable Plasmid in Schedule 4 of the SUSDP.

XXXX has confirmed that the application for registration has been considered by XXXX.

XXXX.

The Committee also reaffirmed its view that it was essential that use of GHRH Injectable Plasmid be under the close supervision of a veterinarian.

DECISION 2007/49- 10

The Committee agreed to confirm the foreshadowed decision taken at the October 2006 meeting that GHRH Injectable Plasmid be included in Schedule 4 of the SUSDP noting the need for veterinary supervision.

Schedule 4 – New entry

GHRH INJECTABLE PLASMID.

4.6 2,4-DICHLOROPHENOXYACETIC ACID

PURPOSE

The Committee considered the scheduling of 2,4-Dichlorophenoxyacetic Acid (2,4-D)

BACKGROUND

At the October 2006 NDPSC meeting, the Committee considered the scheduling of 2,4-D following review under the APVMA's Chemicals Review Program. XXXX reported the following as part of the review of 2,4-D.

Acute Toxicity

XXXX

In their pre-meeting submission. XXXX noted the following.

XXXX

The Committee agreed that changes to the scheduling of 2,4-D may have some regulatory implications as PubCRIS listed 168 registered products. The Chemical Review outcomes had not yet been concluded by the APVMA and it was understood that the focus of their attention at this time had been on the environmental concerns that were also identified as part of the review. It was suggested that if the NDPSC were to foreshadow changes to the scheduling of 2,4-D as suggested by XXXX, then the final outcome of the review could also reflect the scheduling outcomes including the expected industry comment.

The Committee agreed to foreshadow that, based on its acute toxicity, 2,4-D be included in Schedule 6 of the SUSDP with a cut-off to Schedule 5 for 2,4-D in preparations containing 20 per cent or less of 2,4-D.

DISCUSSION

The Committee noted that XXXX had lodged a post-meeting submission in response to the Committee's foreshadowed proposal to amend the scheduling of 2,4-D.

XXXX commented that:

- 2,4-D is still currently under review by the APVMA.
- XXXX

The Committee was advised that the APVMA had indicated that the overall review of 2,4-D may not be concluded until the end of 2007.

The Committee agreed that it would be desirable to conclude all considerations on 2,4-D at the same time. However, the Committee also noted that public health concerns had been identified and that it was desirable that these be addressed as soon as possible. However, the Committee agreed that the scheduling decision on 2,4-D be deferred until the June 2007 meeting when the extent of progress by the APVMA on the wider review of 2,4-D would be known. In this regard, the Committee requested XXXX to provide to the Committee at its June 2007 meeting, an overview of the review of 2,4-D, including progress, timing of review/outcomes, issues identified etc.

OUTCOME

The Committee agreed that having regard to the ongoing review of 2,4-D by the APVMA, the decision to revise the scheduling of 2,4-D be deferred until the June 2007 meeting.

4.7 DICHLORPROP-P

PURPOSE

The Committee considered the scheduling of dichlorprop-P.

BACKGROUND

At the NDPSC's October 2006 meeting, the Committee noted XXXX had sought XXXX of the synthetic phenoxy herbicide dichlorprop- XXXX the single R-(+) stereoisomer of dichlorprop (termed dichlorprop-P). XXXX

The Committee received XXXX of the XXXX . XXXX noted the following:

XXXX

XXXX suggested that the entry in the SUSDP be: "Dichlorprop-P (the R-enantiomer)".

Comment from XXXX was to the effect that they supported dichlorprop-P being included in Schedule 5.

The Committee agreed that, given the potential for severe eye irritancy, 2,4 dichlorprop (including the R and S enantiomers) be included in Schedule 6 of the SUSDP.

DISCUSSION

The Committee received post-meeting comment from XXXX.

XXXX

XXXX has proposed that the scheduling entry be:

Schedule 5

2,4-DICHLORPROP (includes the R and S enantiomers) in preparations containing 5 per cent or less of 2,4-dichlorprop for the use as a plant growth regulator.

However, XXXX assessment disagreed with XXXX classification of the product as a slight-to-moderate eye irritant. XXXX considered that this product should be classified as a severe eye irritant as originally stated in XXXX assessment report as it fits the

toxicology profile of a Schedule 6 substance. In regard to the eye irritancy, XXXX had also sought external advice from XXXX.

A member questioned the need to include reference to the R- and S- enantiomers in the SUSDP schedule entry given that Part 1 (2) (e) of the SUSDP notes that scheduled entries also include every stereoisomer of the substance and every salt of the stereoisomer. The Committee requested the Secretariat to investigate why a specific reference to the R and S enantiomers for 2,4-dichlorprop had been listed in the SUSDP, and if necessary, develop for the Committee's consideration, a policy against which enantiomers could be considered in future.

OUTCOME

The Committee confirmed Decision 48/8 taken at the October 2006 meeting that, given the potential for severe eye irritancy, 2,4-dichlorprop (including the R-and S-enantiomers) be included in Schedule 6 of the SUSDP, noting an editorial change under Item 21.1.1.

5. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

5.1 SUSDP, PART 4

5.1.1 HYDROCARBONS, LIQUID

PURPOSE

The Committee considered the scheduling of hydrocarbon liquids.

BACKGROUND

XXXX submitted an application to exempt from scheduling very small volumes of liquid under the Schedule 5 entry for hydrocarbons, liquid.

XXXX submitted XXXX transfluthrin liquid to repel mosquitos. The product is XXXX

The product is exempt under the Schedule 6 transfluthrin entry:

TRANSFLUTHRIN **except**:

(a) in preparations containing 1 per cent or less of transfluthrin; or
(b) in a cartridge for vaporiser use containing 600 mg or less of transfluthrin per cartridge.

However, as the product is approximately 90% hydrocarbon solvent, it will be classified as Schedule 5.

CONSIDERATIONS

XXXX believe that, based on the exceptions under the Schedule 5 entry for hydrocarbons, liquid:

- the product in question does not warrant scheduling; and
- given exception *(h) for writing correction fluids and thinners for writing correct fluids packed in containers having a capacity of 20 mL or less*, an additional exception for very small volumes for other products is appropriate.

XXXX therefore requested that the NDPSC consider an additional exception to the hydrocarbons liquid Schedule 5 entry to cover very small volumes of liquid:

(i) when packed in containers each containing less than 2 mL.

The November 1991 DPSC Meeting agreed to exempt from scheduling liquid hydrocarbons when used as a solvent in writing correction fluids packed containers having a capacity of 20 mL or less.

The February 1998 NDPSC Meeting agreed to exempt from scheduling liquid hydrocarbons when used as thinners for writing correction fluids packed in containers having a capacity of 20 mL or less.

During discussions at the 1991 and 1998 Meetings, the Scheduling Committees noted that the volume, style of container and nature of the product made ingestion unlikely. However, they also noted that like all solvents, the potential for inhalation abuse existed and therefore also agreed to reconsider if a need was demonstrated in the future.

The Committee was advised by the Secretariat that XXXX had emailed their submission to the NDPSC Secretariat on 29 September 2006, but that the application had been misfiled resulting in its omission from the February 2007 pre-meeting gazette notice.

A Member informed the Meeting that a policy of the Committee was to sight such products before making a scheduling decision.

OUTCOME

The Committee agreed to foreshadow a Schedule 5 amendment to exempt small volumes of hydrocarbons liquid when packed in containers each containing less than 2 mL. The Committee also agreed that a sample of the product be sought from the applicant for viewing at the June 2007 NDPSC Meeting.

FORESHADOWED DECISION (for consideration at the June 2007 Meeting)

Schedule 5 – Amend entry

HYDROCARBONS, LIQUID, including kerosene, diesel (distillate), mineral turpentine, white petroleum spirit, toluene, xylene and light mineral and paraffin oils (but excluding their derivatives), **except**:

(a) toluene and xylene when included in Schedule 6;

(b) benzene and liquid aromatic hydrocarbons when included in Schedule 7;

(c) food grade and pharmaceutical grade white mineral oils;

(d) in solid or semi-solid preparations;

(e) in preparations containing 25 per cent or less of designated solvents;

(f) in preparations packed in pressurised spray packs;

(g) in adhesives packed in containers each containing 50 grams or less of adhesive;

(h) in writing correction fluids and thinners for writing correction fluids packed in containers having a capacity of 20 mL or less; or

(i) when packed in containers each containing less than 2 mL.

5.2 SUSDP, PART 5

5.2.1 APPENDIX J

PURPOSE

The Committee considered progress in addressing the future arrangements for substances in Appendix J and the foreshadowing of amendments to the scheduling of 4-aminopyridine and zinc phosphide in line with recommendations from the APVMA.

BACKGROUND

At the June 2005 NDPSC meeting the Committee agreed to maintain the current Appendix J introduction for the time being and await the outcome of the APVMA review. The Members also agreed that the way to take the Appendix J issue forward was to:

- Obtain the APVMA review of agvet chemicals listed in Appendix J when it becomes available;
- Finalise the list of substances in Appendix J controlled by APVMA as RCPs;
- Examine the fundamentals of Appendix J setting out clearly what the intention of Appendix J is, the controls and conditions placed on Appendix J substances, and what it is endeavouring to deliver to the jurisdictions;
- Determine the status of substances in Appendix J excluding those controlled by APVMA, including whether controls are necessary or dealt with elsewhere (it was suggested that the Office of Chemical Safety (OCS) could assist - Members acknowledged that this could be a difficult but necessary exercise);
- Decide if particular substances should be removed from Appendix J; and
- Re-examine the introduction of Appendix J with a view to ensuring the conditions of availability for use directly reflect the desired controls for either individual substances or groups of substances.

At the October 2006 NDPSC meeting, the APVMA provided a copy of the draft report entitled 'Project to address inconsistencies between substances listed in Appendix J of the SUSDP and products declared as Restricted Chemical Products' and advised that the draft report represented Phase 1 of the review which had now been completed in accordance with the undertakings described above. Phase 2 was seen by the APVMA as a separate project which would address the RCP status of individual products and the type of training and accreditation etc necessary in response to the degree of risk identified. This would require further consideration by individual States/Territories and the APVMA.

The Committee also noted the draft report's conclusion that the extrapolated acute toxicity of XXXX was commensurate with a Schedule 6 poisons schedule. The report suggested that the NDPSC may wish to consider amendments which would include grain based products containing 25 g/kg or less of zinc phosphide in Schedule 6.

Similarly, the extrapolated acute toxicity of 4-aminopyridine in XXXX was considered by APVMA to be commensurate with a Schedule 6 poisons schedule. The APVMA further suggested that the NDPSC consider amendments which would include grain based products containing 5 g/kg or less of 4-aminopyridine in Schedule 6.

The Committee supported the ongoing process for consultation and agreed that individual jurisdictions should provide comment to the APVMA through the NDPSC Secretariat by 3 November 2006.

The Committee also agreed to foreshadow consideration of the scheduling of 4-aminopyridine and zinc phosphide at the February 2007 NDPSC Meeting.

The APVMA has now advised that:

- A draft Project report was tabled at the 31st meeting of the Registration Liaison Committee (RLC) in September 2006 and at the 48th meeting of this Committee (NDPSC) in October 2006. Comments on the report and the proposed approach were sought from State and Territory members of RLC and from jurisdictional members of this Committee. Comments have since been received.
- Based on the comments received, the draft report is now being finalised for posting to the APVMA website. An Industry consultation period of 1 month will follow.
- When the finalised report becomes available, a copy will be formally referred to this Committee for its consideration of the scheduling recommendations.
- Upon completion of this project, the APVMA will initiate a related project on the declaration of RCPs. The APVMA will provide the Committee with regular updates on the progress of this related project.

DISCUSSION

The Committee considered what steps, if any, needed to be taken to progress further consideration of Appendix J, noting that the APVMA report was soon to be made public after which a further phase of the project on the declaration of RCPs was planned. The Committee was advised that Phase 2 of the project could take some years to complete and implement. Consequently, further action in respect to the broad consideration of Appendix J was deferred until Phase 2 of the APVMA project was well underway or concluded.

The Committee also considered including in the pre-meeting Gazette Notice for the June 2007 meeting, a proposal to amend the scheduling of zinc phosphide and 4-aminopyridine in line with the specific APVMA recommendations as outlined in the report to the Committee in October 2006.

OUTCOME

The Committee again noted the report and recommendations of the APVMA report addressing inconsistencies between substances listed in Appendix J of the SUSDP and products declared as restricted chemical products.

Noting that the APVMA report was soon to be released for public comment and that the report concludes that the extrapolated toxicity data for 4-aminopyridine and zinc phosphide support their inclusion in Schedule 6 of the SUSDP, the Committee agreed to include a proposal to amend the scheduling of 4-aminopyridine and zinc phosphide in the pre-meeting gazette notice for the June 2007 meeting.

FORESHADOWED DECISION (For consideration at the June 2007 meeting)

4-Aminopyridine

Schedule 7 - Amendment

4-AMINOPYRIDINE **except** when included in Schedule 4 or Schedule 6.

Schedule 6 – New Entry

4-AMINOPYRIDINE in preparations containing 0.05 per cent or less of 4-aminopyridine.

Schedule 4

4-AMINOPYRIDINE for therapeutic use.

Phosphides, Metallic (To be cross- referenced to Zinc Phosphide)

Schedule 7 - Amendment

PHOSPHIDES, METALLIC **except** when included in Schedule 6.

Schedule 6 – New Entry

PHOSPHIDES, METALLIC when included in preparations containing 2.5 per cent or less of metallic phosphides.

6. MATTERS REFERRED BY THE AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY.

6.1 BIFENTHRIN

PURPOSE

The Committee considered the scheduling of bifenthrin.

BACKGROUND

XXXX

Bifenthrin is currently listed in Schedule 7 with a 10% cut-off to Schedule 6. It is exempt from scheduling in preparations containing 0.5% or less. XXXX, the NDPSC considered amending the existing Schedule 6 cut-off for 10% or less bifenthrin preparations, to 25% or less bifenthrin preparations.

DISCUSSION

The Committee noted that XXXX and XXXX had advised of their specific interest in the outcome of the Committee's deliberations.

A member noted that, while not applying to the submission before the Committee in relation to bifenthrin, there was an increasing trend whereby applicants sought scheduling cut-offs for products on the basis of extrapolation of the data provided in support of the substance per-se. The member noted that if this trend continued, then supporting data would not be available and, in the absence of data, there was a likelihood of 'over scheduling'. The member sought the Committee's advice on the appropriateness of extrapolating data. The Committee agreed that applicants should be encouraged to provide data. Extrapolation of data was to be limited to circumstances where the use of such data is justifiable.

DECISION 2007/49 - 11

Based on the oral toxicity of bifenthrin, the Committee agreed that the Schedule 6 entry for bifenthrin could be amended to accommodate a cut-off of 25 per cent.

Schedule 6 - Amendment

BIFENTHRIN – Amend entry to read:

BIFENTHRIN in preparations containing 25 per cent or less of bifenthrin **except** in preparations containing 0.5 per cent or less of bifenthrin.

6.2 BETACYFLUTHRIN

PURPOSE

The Committee considered the scheduling of betacyfluthrin.

BACKGROUND

XXXX

Betacyfluthrin is currently in Schedule 7, with preparations containing 12.5% or less in Schedule 6 and in aqueous preparations containing 2.5% or less in Schedule 5. XXXX had undertaken a Health Risk Assessment of the data submitted in support of XXXX

XXXX

XXXX suggested that the NDPSC may consider betacyfluthrin in XXXX With the requested scheduling change, XXXX suggested that the entry for betacyfluthrin in

Schedule 5 be amended to read: betacyfluthrin – (a) in aqueous preparations containing 2.5% or less of betacyfluthrin, or (b) in solid preparations containing 8% or less of betacyfluthrin in a plastic matrix.

DECISION 2007/49 - 12

The Committee agreed to amend the scheduling of betacyfluthrin to include solid preparations containing 8 per cent or less of betacyfluthrin in a plastic matrix in Schedule 5 of the SUSDP, noting the low dermal toxicity and the extrapolated low oral and inhalation toxicity and slight skin and eye irritancy.

Schedule 5 – Amendment

BETACYFLUTHRIN – Amend entry to read:

BETACYFLUTHRIN:

(a) in aqueous preparations containing 2.5 per cent or less of betacyfluthrin; or

(b) in solid preparations containing 8 per cent or less of betacyfluthrin in a plastic matrix.

6.3 HYDROCORTISONE ACEPONATE

PURPOSE

The Committee considered the scheduling of hydrocortisone aceponate.

BACKGROUND

XXXX have submitted data in support of approval of the active constituent, hydrocortisone aceponate, XXXX Hydrocortisone aceponate belongs to the class of corticosteroid hormones which are often used to relieve inflammation (swelling, heat, redness, and pain) and treat certain forms of arthritis and other disorders XXXX

DISCUSSION

The Committee noted that hydrocortisone (and derivatives) is currently a Schedule 4 poison for non-human therapeutic use. The use-pattern and characteristics of XXXX, indicated that NDPSC may wish to consider the specific inclusion of hydrocortisone aceponate in Schedule 4 of the SUSDP.

XXXX

Based on the consideration that hydrocortisone aceponate is a new therapeutic substance and is for ailments or symptoms that require professional veterinary diagnosis, the NDPSC considered hydrocortisone aceponate appropriate for specific inclusion in Schedule 4 of the SUSDP.

DECISION 2007/49 - 13

The Committee agreed to include hydrocortisone for veterinary use in Schedule 4 of the SUSDP noting the need for veterinary supervision in its use. However, it was considered appropriate that all hydrocortisone salts intended for veterinary use in dogs should be included. Consequently, the existing Schedule 4 entry for hydrocortisone (and which includes all salts) would be amended appropriately.

Schedule 4 - Amendment

HYDROCORTISONE – Amend entry to read:

HYDROCORTISONE:

(a) for human use **except** when included in Schedule 2 or 3; or

(b) for veterinary use in dogs.

6.4 PYRASULFATOLE

This item was withdrawn by XXXX prior to the meeting.

6.5 PROCYMIDONE

PURPOSE

The Committee considered the scheduling of procymidone.

BACKGROUND

At its February 2004 meeting, the NDPSC considered the scheduling of procymidone. The Committee noted the OCS evaluation report which had identified procymidone as a XXXX and recommended that an entry in Schedule 7 of the SUSDP for procymidone was appropriate. XXXX Accordingly, the Committee considered the scheduling of procymidone remained appropriate.

XXXX had now submitted supplementary data to update the database for procymidone. XXXX had also requested a reconsideration of the scheduling of procymidone.

DISCUSSION

XXXX provided an assessment of the XXXX toxicology submitted by XXXX

XXXX

Accordingly, XXXX suggested that the current Schedule 7 classification for procymidone remained appropriate.

The Committee noted that continuing the status quo would not prevent further consideration of the existing scheduling of procymidone should further argument of data be presented.

The Committee noted that XXXX had noted a specific interest in the outcome of the Committtee's consideration of the scheduling of procymidone.

OUTCOME

Having regard to the possibility of developmental effects, the Committee agreed that there be no change in the scheduling of procymidone and that procymidone continue to be included in Schedule 7 of the SUSDP.

7. MATTERS REFERRED BY THE OFFICE OF CHEMICAL SAFETY (OCS) OR THE NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

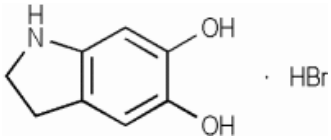
7.1 5,6-DIHYDROXYINDOLINE

PURPOSE

The Committee considered the scheduling of 5,6-dihydroxyindoline.

BACKGROUND

5,6-Dihydroxyindoline (which correlates with the current marketing name) is also known as 1H-Indole-5,6-diol, 2,3-dihydro. The structure of the hydrobromide salt is:



DISCUSSION

A new industrial chemical (5,6-dihydroxyindoline HBr) was recently assessed under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). The

assessment report included a recommendation that the Committee should consider 5,6-dihydroxyindoline HBr for scheduling. Members noted the following from the assessment report:

- 5,6-Dihydroxyindoline HBr will be a component of ready to use hair products, including hair dyes, at a maximum concentration of 2%.

Pharmacokinetic

- When 5,6-dihydroxyindoline HBr was topically applied (to rats) as a part of a hair dye for 30 minutes, ~10% was absorbed to the skin and ~1% was biovailable for systemic exposure. Most was eliminated from the body 72h after application. No information was available about the metabolism of 5,6-dihydroxyindoline HBr and the presence or effects of metabolic products. However, 5,6-dihydroxyindoline HBr has a propensity to oxidise and undergo rearrangement/oxidative polymerisation to melanin, so it was possible that some of the systemically available 5,6-dihydroxyindoline HBr may form melanin deposits in some organs (such as kidney and femur, as determined by a 14C study).

Toxicological information

Endpoint and Result	*Test substance*	*Assessment Conclusion*
Rat, acute oral	5,6-dihydroxyindoline	harmful LD_{50}: 868mg/kg bw for males 368 mg/kg bw for females
Rabbit, skin irritation	HBr salt	slightly irritating
Rabbit, eye irritation	HBr salt	severely irritating
Guinea pig, skin sensitisation – non-adjuvant test.	HBr salt	inadequate evidence of sensitisation
Guinea pig, skin sensitisation – adjuvant test	HBr salt	evidence of sensitisation
Rat, repeat dose oral toxicity – 90 days	HBr salt	NOAEL: 20 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days	HBr salt	NOAEL: 20 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days	HBr salt	NOAEL: 20 mg/kg bw/day
Analysis of organs from the repeat dose toxicity studies	HBr salt	LOAEL: 10 mg/kg bw/day
Genotoxicity – bacterial reverse mutation with DMSO solvent	HBr salt	mutagenic
Genotoxicity – bacterial reverse mutation with water solvent	HBr salt	mutagenic
Genotoxicity – mutagenicity in Chinese Hamster V79 cells in vitro	HBr salt	equivocal
Genotoxicity – in human lymphocytes in vitro	HBr salt	non genotoxic
Genotoxicity – in vivo in mouse polychromatic erythrocytes	HBr salt	non clastogenic
Genotoxicity – in vivo hepatocyte DNA repair test	HBr salt	non clastogenic

Dermal absorption/penetration in vitro with 0.1% 5,6-dihydroxyindoline HBr in the cosmetic formulation	HBr salt	<5% absorption 0.4% bioavailable
Pharmacokinetic studies of dermally applied hair dye on rats (1% 5,6-dihydroxyindoline HBr)	HBr salt	<10% absorption 0.77% bioavailable

- It was noted that in generating the acute oral results all animals dosed at 2000 mg/kg bw died within the first 3 days. All the female rats died after being dosed at 1000 mg/kg bw. No abnormalities were detected in animals dosed at 200mg/kg bw.
- For the eye irritation tests it was noted that 5,6-dihydroxyindoline HBr is severely irritating to the eyes based on appearance of irreversible signs of necrosis in the conjunctivae, and corneal epithelial damage observed up to day 15 post treatment. It was classified as a severe eye irritant.
- Based on a maximisation study in guinea pigs, 5,6-dihydroxyindoline HBr also had skin sensitisation potential. There was a clear sensitisation reaction in animals challenged with 5% and some sensitisation responses in animals challenged with 1% 5,6-dihydroxyindoline HBr. Based on these results 5,6-dihydroxyindoline HBr was classified as a skin sensitiser.
- Based on the results of three repeat dose oral toxicity studies in rats 5,6-dihydroxyindoline HBr would be classified as posing danger of cumulative effects.
- Considering the evidence of all tests 5,6-dihydroxyindoline HBr was not classified as mutagenic. No studies evaluating carcinogenicity or reproductive toxicity of 5,6-dihydroxyindoline HBr were available. The notifier advised that no adverse health effect arising from human exposure have been observed or reported.

Hazard

- Based on the available data 5,6-dihydroxyindoline HBr was classified as hazardous under the NOHSC Approved Criteria for Classifying Hazardous Substances. The classification and labelling details were:
  - R22 Harmful if swallowed
  - R33 Danger of cumulative effects
  - R41 Risk of serious damage to eyes
  - R43 May cause sensitisation by skin contact
- The classification using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) was:

	Hazard category	***Hazard statement***
Acute toxicity	4	Warning: Harmful if swallowed
Serious eye damage/eye irritation	1	Danger: Causes severe eye damage
Skin sensitisation	1	Warning: May cause an allergic skin reaction

Overseas Opinion

- The Scientific Committee on Cosmetic and Non-food Products (SCCNFP) was of the opinion that "Dihydroxyindoline HBr does not pose a health risk when used as a semi-permanent hair dye at concentrations not exceeding 2.0 %" (SCCNFP/0669/03).
- The SCCNFP also gave an opinion on the use of dihydroxyindole (the likely metabolite of dihydroxyindoline HBr) in cosmetic products (SCCNFP/0657/03). Based on the data package submitted for dihydroxyindole, the margin of safety for use in hair dyes did not appear to be adequate. However, concerns were expressed about the quality and the outcomes of the one 13-week oral repeat dose study, the mutagenicity/genotoxicity studies and the one skin penetration study. The opinion of the SCCNFP concerning dihydroxyindole was that: "The SCCNFP is of the opinion that dihydroxyindole is not suitable for use in hair dyes". However, these results cannot be adequately linked to possible effects of 5,6-dihydroxyindoline HBr, as a much more comprehensive and quality data set was provided for 5,6-dihydroxyindoline HBr.

Exposure

- The public will be exposed to 5,6-dihydroxyindoline HBr at a maximum concentration of 2% through use of hair dyes. At this concentration it was unlikely to be a skin irritant but it was expected to be an eye irritant. It was also expected to cause skin sensitisation effect upon repeated use. Therefore the risk of local adverse effects when using hair dye products containing 2% of 5,6-dihydroxyindoline HBr was significant. The risk may be lower for preparations containing <1% 5,6-dihydroxyindoline HBr, however a quantitative risk assessment cannot be carried out for sensitisation on the basis of available studies. The risk could be better estimated if a local lymph node assay (LLNA) was available for 5,6-dihydroxyindoline HBr, and the incidence of sensitisation in use should be closely monitored.
- The product labelling currently advises that the product may cause an allergic reaction and to avoid contact with the eyes. A preliminary skin test is also advised which should identify individuals susceptible to sensitisation.

Cumulative effects

- Based on the repeated oral dose exposure study, a risk exists for accumulation of pigment deposits in kidneys and duodenum for repeated dermal application of formulations containing ≥ 1% 5,6-dihydroxyindoline HBr. The risk may be lower for dermal application because of the relatively low absorption of 5,6-dihydroxyindoline

HBr. These pigment deposits appear not to have significant physiological effects in the 90-day oral dose study, but long-term effects on the organs have not been examined and the risk of adverse effects cannot be excluded. Inclusion of an advisory statement that would inform consumers of the risk of cumulative effects at high exposure levels under certain conditions of use will be included on the unit label and the leaflets for the hair dye products containing 5,6-dihydroxyindoline HBr.

NICNAS Conclusion

- There is no significant concern to public health when used in the proposed manner and provided the hair dye formulations {i.e. < 2% 5,6-dihydroxyindoline HBr} are adequately labelled to indicate skin sensitisation and eye irritation potential.

NICNAS Recommendations

- The NDPSC should consider 5,6-dihydroxyindoline HBr for scheduling. (Members noted that NICNAS made no recommendation as to which Schedule or Schedules would be appropriate. The Secretariat did confirm with the evaluator, however, that while most of the toxicological data was for the specific HBr salt, the main risks appeared to be related to the 5,6-dihydroxyindoline. The evaluator therefore agreed that the Committee should give consideration to a broader entry to cover all derivatives i.e. 5,6-dihydroxyindoline.)
- Products containing 5,6-dihydroxyindoline HBr and available to the public must carry the following safety directions on the packaging label and the use directions:
    - WARNING: This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.
    - USE AS DIRECTED. May cause cumulative effects if use exceeds the recommended application volumes and/or pattern.
    - If in eyes wash out immediately with water.
    - Keep out of reach of children.(Members noted that, although worded as mandatory requirements, NICNAS had no ability to enforce such labelling, and that the above should instead be read as a recommendation for consideration by the NDPSC. NICNAS also confirmed that the statement regarding cumulative effects was endorsed by the applicant.)
    - 5,6-Dihydroxyindoline HBr should not be used in personal cosmetic products in concentration >2%.

Members noted that the XXXX pre-meeting comment referred to the NICNAS recommendation and asserted that should the scheduling outcome be similar to phenylenediamines, toluenediamines and Basic Orange 31, then the substance should be included in the Committee's considerations under Item 8.2.

The Committee discussed NICNAS's proposal to include a warning statement regarding possible cumulative effects of 5,6-dihydroxyindoline. A Member did not support this proposal and asserted that the SUSDP already had sufficient warning statements to control the risks of this substance. Additionally, another Member noted that any possible cumulative effect, according to the NICNAS report, would be for higher concentrations when used cosmetically. Members agreed that it was more appropriate to control this risk by restricting access to >2% for cosmetic use through the Appendix C entry (which was also based on the acute oral toxicity, severe eye irritancy and evidence of sensitisation) than through use of an new warning statement.

A Member queried whether cosmetic use ≤ 2% could be exempted through reverse scheduling controls analogous to hair dyes in the phenylenediamines and toluenediamine Schedule 6 entries. The Committee noted that this would not be appropriate as the toxicology profile of 5,6-dihydroxyindoline included acute oral and eye irritancy risks considerably higher than phenylenediamine and toluenediamine. Additionally, 5,6-dihydroxyindoline was a new substance and Members would like market experience of the material before it would be possible to consider a reverse scheduling option.

DECISION 2007/49 - 14

The Committee agreed:

- that scheduling should apply to all derivatives of 5,6-dihydroxyindoline, not just the hydrobromide and that scheduling should use the synonym which correlated to the commercial name (5,6-dihydroxyindoline) rather than the name predominately used in the NICNAS assessment (1H-indole-5,6-diol, 2,3-dihydro). For clarity the Committee agreed to cross-reference these two synonyms in the SUSDP index;
- to include 5,6-dihydroxyindoline in Schedule 6 (and Appendix E and F) as the acute oral toxicity, severe eye irritancy and evidence of sensitisation potential constituted a moderate potential for causing harm (when for non-cosmetic uses), the extent of which could be reduced through appropriate packaging and labelling;
- that the data available was insufficient to allow a cut-off for low concentrations to be determined, particularly as the sensitising potential may not be dose dependent and because of the possibility of cumulative effects; and
- that the cosmetic use of > 2% 5,6-dihydroxyindoline posed sufficient danger as to warrant prohibition of sale, supply and use through inclusion in Appendix C.

Schedule 6 – New entry

† 5,6-DIHYDROXYINDOLINE.

Appendix C – New entry

5,6-DIHYDROXYINDOLINE for cosmetic use in preparations containing more than 2 per cent of 5,6-dihydroxyindoline.

Appendix E – Part 2 – New entry

Poison	**Standard Statements**
5,6-Dihydroxyindoline	E1

Appendix F – Part 3 – New entry

Poison	**Warning Statement**	**Safety Directions**
5,6-Dihydroxyindoline	21,28	

SUSDP 23 Index – New entry

1H-INDOLE-5,6-DIOL, 2,3-DIHYDRO
See 5,6-DIHYDROXYINDOLINE

8. OTHER MATTERS FOR CONSIDERATION

8.1 DIMETHICODIETHYLBENZALMALONATE (POLYSILICONE-15)

PURPOSE

The Committee considered the scheduling of dimethicodiethylbenzalmalonate (polysilicone-15) for use in sunscreens.

BACKGROUND

The report of XXXX noted XXXX had recently given consideration to the use of dimethicodiethylbenzalmalonate (polysilicone-15) as a sunscreen active ingredient. A toxicological assessment of dimethicodiethylbenzalmalonate had been undertaken by the TGA.

XXXX report also noted that NICNAS had also approved dimethicodiethylbenzalmalonate for use in cosmetics and hair products up to 10 per cent.

XXXX agreed that polysilicone-15 should be approved for use as a sunscreen active ingredient in listed or registered sunscreen products at a concentration of up to 10 per cent.

There has been no application for the scheduling of dimethicodiethylbenzalmalonate (polysilicone-15).

DISCUSSION

The Committee noted that XXXX had concluded, based on the previously submitted and additional data, that:

- polysilicone-15 has no adverse effects in *in vitro* (previously assessed) or in vivo assays assessing mutagenic/genotoxic potential;
- characterisation of its metabolism using *in silico* analysis indicated a very low likelihood of hazardous degradation products;
- although repeat-dose dermal toxicity was not provided, the negative *in vivo* genotoxicity results lessened the likelihood that polysilicone-15 is carcinogenic. Limited human dermal application data showed that polysilicone-15 has a protective effect against changes associated with possible adverse cellular changes. More than 55,000 kg has been used in the EU over five years, with no reported adverse effects.

It was also noted that XXXX agreed with XXXX conclusions and recommended that polysilicone-15 should be approved for use as a sunscreen active ingredient in listed or registered sunscreen products, at a concentration of up to 10%.

XXXX also noted the NICNAS assessment of polysilicone-15. NICNAS concluded that *"Based on the toxicological data, the notified polymer is expected to be of no concern for human health. The notified polymer is considered to be of low acute oral and dermal toxicity. It is slightly irritating to skin and eyes and did not show any potential for skin sensitisation. There is no toxicological significance for chronic toxicity. The notified polymer is considered to be non-mutagenic, nonphotomutagenic and non-photoclastogenic"*.

DECISION 2007/49 - 15

The Committee agreed that on the basis of low acute oral and dermal toxicity, dimethicodiethylbenzalmalonate (polysilicone-15) for use in cosmetics and sunscreens be included in Schedule 5 of the SUSDP except when in preparations containing 10 per cent or less of dimethicodiethylbenzalmalonate.

The Committee further agreed to cross-reference dimethicodiethylbenzalmalonate to Polysilicone-15 in the next edition of the SUSDP.

Schedule 5 - New entry

DIMETHICODIETHYLBENZALMALONATE **except** when included in preparations containing 10 per cent or less of dimethicodiethylbenzalmalonate.

8.2 LABELLING FOR COMPOSITE PACK HAIR PREPARATIONS INCLUDING THOSE CONTAINING PHENYLENEDIAMINES AND TOLUENEDIAMINE

PURPOSE

The Committee considered the labelling requirements for single use composite pack hair preparations, including those containing phenylenediamines or toluenediamine.

BACKGROUND

The August 2000 NDPSC Meeting agreed to a proposal to exempt hair dyes containing phenylenediamines or toluenediamine conditional upon provision of specified label warnings and standard statements on the product.

At the October 2004 NDPSC Meeting the Committee noted the outcomes of a preliminary review of chemicals in hair dyes and a report on skin and eye irritancy for phenylenediamines and toluenediamine. Based on the outcomes of this report, the Committee agreed to foreshadow amending the Appendix C phenylenediamines entry to include a prohibition on use for eyelash/eyebrow tinting. The Committee further agreed to foreshadow a new Appendix C toluenediamine entry to prohibit its use in eyelash/eyebrow tinting.

The February and June 2005 NDPSC Meetings further considered the eyebrow and eyelash issue, noting that while phenylenediamines and toluenediamine were only moderately irritant to the skin and not corrosive to the eye, they were clearly sensitisers and that the potential risk of causing a strong allergic response in a small number of individuals could be minimised through appropriate labelling. The Committee therefore agreed to amend the Schedule 6 phenylenediamines and toluenediamine entries to allow the use of eyebrow/lash tints in salons and the home when appropriately labelled. Where such labelling was not present these products would be captured by Appendix C.

The June 2006 NDPSC Meeting considered a submission regarding mandatory label requirements for small containers of eyelash/brow tints containing phenylenediamines or toluenediamine. The Committee agreed that:

- as the main risk was sensitisation, which in this case did not demonstrate a clear dose response, strong label warnings were required before such products could be available as Schedule 6; and
- as there was a risk of separation of an outer pack from the immediate container, it was appropriate that all mandatory labelling continued to be applied to the immediate container, regardless of pack size.

DISCUSSION

A Member tabled a proposal regarding the labelling requirements for single use composite pack hair preparations, including those containing phenylenediamines or toluenediamine. The Committee noted the following from this proposal:

Appendix E and F required statements vs. reverse schedule required statements

- The Member asserted that there was need for flexibility in the specified wording for reverse scheduled labelling statements, provided the message was the same.
- The pre-amble for Appendix E and Appendix F state respectively:

Appendix E

"Under poisons legislation, scheduled substances and their preparations are required to be labelled with appropriate directions for first aid attention in case of poisoning. It is the responsibility of the manufacturer, packer and supplier of a drug or poison to ensure that the first aid instructions included on the label of a poison are appropriate for a specific product. The following code has been prepared as a guide for health authorities and manufacturers in drafting suitable first aid directions for this purpose. Standard statements specified in this appendix may be varied provided that the intent is not changed."

Appendix F

"It is the responsibility of the manufacturer, packer and supplier of a drug or poison to ensure that the purchaser or user of a product is given sufficient information to be able to use it correctly and safely.

Under poisons legislation, scheduled substances, which may be harmful to the user, must be labelled with appropriate warning statements and safety directions. The selection of warning statements and safety directions will depend on the formulation of the product, and the use for which it is sold and supplied. The following code has been prepared as a guide for this purpose.

The wording of the warning statements and safety directions specified in this appendix may be varied provided the intent is not changed. Additional statements also may be added to ensure that the user of a product is sufficiently advised of its harmful nature and how to avoid deleterious effects."

- Because the exemptions for hair preparations in the Schedule 6 entries for phenylenediamines and toluenediamine are reverse scheduled, Appendix E and Appendix F, along with the wording flexibility allowed by these appendices, were not applicable. To overcome this inconsistency the Member proposed adding "or words to the effect of" in the relevant paragraphs in the Schedule 6 entries.

Composite packaging

- The majority of hair dyes and bleaching products are fully imported into Australia, and are often sold in composite packaging or kits with multiple components. The

Member asserted that if labelling was different to that required overseas, it necessitated costly separate print and/or production runs, or over-sticking. This was particularly problematic when the labelling was required on both the immediate container and the primary pack, especially for composite packs.

- The Member suggested that when a product was for single use that an exemption could be granted for the immediate container labels of multiple component packs, provided the primary pack label clearly displayed the required statements.
- The Member further suggested that, to avoid any confusion, these requirements (and any permitted exemptions), apply also to bleaching kits, not just 'hair dye preparations', and that the terminology hair preparations be consistently used.

Recommended amendments to the SUSDP

- Part 2 – Labels and Containers, 7.(1)(a) Primary Packs and Immediate Containers:
  - Add a paragraph to exempt the poison if it is a Schedule 5 or Schedule 6 single use composite pack hair preparation, where it is sufficient to label only the primary pack. (Members noted that this exemption would apply to all substances in single use hair preparations in a composite pack, not just phenylenediamines or toluenediamine. Paragraph 7.(1) would only apply if preparations were not compliant with the Schedule 6 phenylenediamines and toluenediamine requirements for being exempt from scheduling.)
- Schedule 6 phenylenediamines:
  - Amend paragraph (c) to "in hair preparations except when the immediate container and primary pack are labelled with the following statements, or words to the effect of:…."
  - Add a new paragraph (e) "in hair preparations in composite packs for single use except where the primary pack is labelled with the following statements, or words to the effect of:…"
- Schedule 6 toluenediamine:
  - Amend paragraph (a), and include a new paragraph (c), directly analogous to the above proposal for phenylenediamines.

Member's noted that XXXX pre-meeting comment supported the above proposal, and contended that the same principles apply for Basic Orange 31 (Item 4.2), 5,6-dihydroxyindoline (Item 7.1) and hair bleaching products. XXXX recommended that a consistent approach be adopted for single use composite pack hair preparations.

Members recalled that the June 2006 NDPSC Meeting noted that the actual wording of Safety Directions and First Aid Instructions in Appendix E and F were not stipulations, they were guidance statements to aid in standardisation. The Committee agreed that there was no need to include new categories in Appendix E and F to account for all variations

resulting from different formulations and that the introduction to both appendices gave enough flexibility and scope for the requested changes. The Committee confirmed that:

- It was the responsibility of the manufacturer, packer and supplier to ensure that the user was given sufficient information to be able to use it correctly and safely.
- Scheduled substances must be labelled with appropriate warning statements and/or safety directions. The selection of warning statements and safety directions will depend on the formulation and use of the product. Appendix E and F were prepared as guides for this purpose.
- The wording of statements specified in Appendix E or F may be varied provided that the intent was not changed. Additional statements may also be added to ensure that the user of a product was sufficiently advised of its harmful nature and how to avoid any deleterious effects.

A Member noted that with regards to allowing flexibility for reverse schedule label statements, there was now a more overt cosmetics regulator – NICNAS – so while compliance remained a State and Territory issue, there would be opportunity to refer reverse schedule label variation issues to NICNAS. Another Member advised, however, that NICNAS does not have a labelling code.

Several Members expressed concern over including the rider "or words to the effect", and questioned how much flexibility this would allow. The Committee generally agreed that it did not wish to be placed in the position of individually approving word variations. Another Member noted that for the Schedule 6 phenylenediamines and toluenediamine entries, there was a very specific risk that the reverse schedule label statements were addressing and the Member would not like to see this message being in any way diluted.

XXXX Member noted that Appendix E and F indicated that similar words could be used provided the intent was not changed. The Member confirmed that XXXX jurisdiction would treat reverse schedule label wording in the same way. The Member observed, however, that this would be on a case-by-case basis, and that the Member would not be comfortable with "or words to the effect". The Member asserted that industry may be unduly concerned, and that a sponsor could go to a jurisdiction to get an exemption from exact wording requirements.

A Member suggested that flexibility in the wording of reverse scheduling labels could be addressed by including a statement under "Principles of Scheduling – Reading the Schedules" that indicated that the variation allowed under Appendix E or F would also apply to reverse schedule labels. The Committee agreed to foreshadow consideration of this issue at the June 2007 NDPSC Meeting, and further agreed that the Drafting Advisory Panel should develop a draft paragraph out-of-session.

Until the Committee was able to see examples of these composite packs that would only need labelling on the primary pack it did not support the proposal to amend labelling

requirements so that Schedule 5 or Schedule 6 poisons in a single use composite pack hair preparation would only need to label the primary pack.

The Committee also did not support amending various references to 'hair dyes' (e.g. in the Schedule 6 phenylenediamines entry) to 'hair preparations' as there was potential for inadvertent capture of products for non-dying use patterns.

OUTCOME

The Committee confirmed:

- the current phenylenediamines and toluenediamine Schedule 6 entries, and
- the current paragraph 7.(1) of the SUSDP.

The Committee also agreed to foreshadow consideration at the June 2007 NDPSC Meeting of an amendment to the "Principles of Scheduling" to explain the Committee's intent regarding flexibility for the wording of reverse schedule label statements.

FORESHADOWED DECISION (for consideration at the June 2007 Meeting)

PRINCIPLES OF SCHEDULING - READING THE SCHEDULES - Amendment
(New paragraph to be inserted after the 5th existing paragraph).

Where a schedule entry for a poison requires a specific statement to be included on a label as a condition for a product to qualify for an exemption ('reverse scheduling'), then in cases where it is impracticable for a supplier to use the exact wording of such a statement, its wording may be varied provided that the full intent and meaning of the statement is not changed.

PHARMACEUTICALS

10. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (POST-MEETING SUBMISSIONS UNDER 42ZCY)

10.1 FLUORIDE

PURPOSE

The Committee considered post-meeting comments received in response to the October 2006 NDPSC Meeting decision (2006/48-13) on the scheduling of fluorides.

BACKGROUND

Prior to June 2004 the fluorides Schedule 2 entry was:

> FLUORIDES for human therapeutic use (except in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):
>
> (a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or
>
> (b) in preparations for topical use containing 2.5 per cent or less of fluoride ion except:
>
> (i) Dentrifices included in Schedule 3;
>
> (ii) Dentrifices containing 1000 mg/kg or less of fluoride ion; or
>
> (iii) other dental hygiene products containing 100 mg/kg or 100 mg/L or less of fluoride ion.

The 1000 mg/kg Schedule 2(b)(ii) exemption for dentrifices, and the general Schedule 2 exemption for ≤ 15 mg/kg were introduced at the February 1986 DPSSC Meeting. Dentrifices with > 1000 mg/kg fluoride ion were included in Schedule 3 at the July 1987 DPSSC Meeting. The 2.5 % cut-off in part (b) of the Schedule 2 entry resulted from a February 2001 NDPSC decision to harmonise with New Zealand.

The February 2004 NDPSC Meeting agreed to exempt dental hygiene products which were not dentrifices (such as mouth rinses) containing ≤ 220 mg/kg fluoride ion, conditional upon a 120 mg pack size, child-resistant closure (CRC) and label warnings against swallowing the product and use in children under six. Non-compliant

preparations were included in Schedule 2. The June 2004 NDPSC Meeting varied this decision by replacing "for human therapeutic use" in the fluoride entries with "for human use". No Committee discussion was minuted regarding those non-therapeutic products for human use which were now captured e.g. fluoride containing dental whiteners.

The Committee considered some minor changes to the Schedule 2 and Schedule 4 entries at the February, June and October 2005 NDPSC Meetings as a consequence of the introduction of the *Required Advisory Statements for Medicines Labels* (RASML).

The June 2006 NDPSC Meeting was advised by a Member that it appeared that the June 2004 amendment to the Schedule 2 fluorides entry had a wider regulatory impact than intended. Members agreed to gazette consideration of this issue at the October 2006 NDPSC Meeting.

Prior to the October 2006 NDPSC Meeting all topical dental whiteners or bleaches which do not also make an oral hygiene claim with 15 mg/kg(L) > fluoride < 2.5% would be Schedule 2. Where a topical dental whitener or bleach also has an oral hygiene use the product would either qualify for an exemption under (b)(i),(ii),(iii) or (iv) or would be Schedule 2. Those with 15 mg/kg(L) > fluoride < 220 mg/kg(L) and not excluded by (b)(i) or (ii) would be captured under part (b)(iii) or (iv) - depending on whether or not they were therapeutic goods - by virtue of not being fitted with a CRC or labelled with the appropriate labelling. Where the CRC and labelling requirements were fulfilled such products would not be scheduled.

The October 2006 NDPSC Meeting agreed:

- That pastes, powders or gels containing 15 mg/kg < fluoride ion ≤ 1000 mg/kg for all applications to teeth (including dental hygiene, whitening and bleaching) did not warrant scheduling as there was little risk of these formulations being ingested in sufficient quantities to cause harm. Members therefore agreed to amend Schedule 2(b)(ii), Schedule 4(b), Schedule 5(b) and Schedule 6(b) by replacing the current wording with "dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion".
- Confirmed that it was appropriate that all pastes, powders or gels for use on teeth containing > 1000 mg/kg fluoride be controlled by the Schedule 3 entry as the risks from this concentration of fluoride ion required pharmacist advice. Members therefore agreed to amend Schedule 3 by replacing the current wording with "dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing more than 1000 mg/kg of fluoride ion".
- Agreed that other formulation types (i.e. not pastes, powders or gels) for topical oral use containing 220 mg/kg < fluoride ion ≤ 2.5 % (including dental hygiene and whitening) were to be Schedule 2 due to the increased risk of such formulations being ingested in a quantity which may cause harm.

- Agreed that the public health risks of topical dental hygiene, whitening or bleaching products containing 15 mg/kg < fluoride ion ≤ 220 mg/kg (except as specified by (b)(ii) in the Schedule 2 fluorides entry) would be acceptably minimised through labelling, pack size limitations and a CRC requirement. Where these conditions were not met, capture by Schedule 2 was appropriate. Members therefore agreed to amend Schedule 2(b)(iii) and (iv), Schedule 4(c) and (d), Schedule 5 (c) and (d) and Schedule 6 (c) and (d) to allow dental whiteners and bleachers to qualify for these exemptions by adding ", whitening or bleaching" after the existing "other dental hygiene".

DISCUSSION

Members noted a XXXX post-meeting comment, which included:

- XXXX noted that replacing the term "dentifrice" with "pastes, powders or gels for the cleaning of teeth" in the fluoride entries (except for Schedule 3 which was amended to "pastes, powders or gels for use on teeth") caused the inadvertent capture of products for use on teeth, but not for cleaning of teeth, containing 1000 mg/kg < fluoride ≤ 2.5% in both Schedule 2 and Schedule 3.
- The October 2006 NDPSC Meeting resolved this inconsistency by confirming that the scheduling for all pastes, powders or gels for use on teeth containing > 1000 mg/kg was Schedule 3. XXXX asserted that this decision did not acknowledge that many of the products that were inadvertently captured in both Schedule 2 and Schedule 3 had been supplied as Schedule 2 products for many years, without any evidence of concerns that would require further restriction to their access by moving them to Schedule 3. [The Committee generally confirmed that, although asserted to be Schedule 2, these products should have been Schedule 3 i.e. when a product was captured by multiple schedules, inadvertently or otherwise, the more restrictive schedule should be applied.]
- XXXX asserted that these products, which are supplied in pharmacy, are primarily purchased by patients at the recommendation of their treating dentist.
- XXXX also noted that the Committee agreed that other formulation types (not pastes, powders or gels) for topical oral use containing 220 mg/kg < fluoride ion ≤ 2.5% (including dental hygiene and whitening) were to be Schedule 2 due to the increased risk of such formulations being ingested in a quantity which may cause harm. XXXX asserted that this seemed inconsistent, from a risk perspective, with the proposal to move dental hygiene products that are pastes, powders or gels that are for uses other than cleaning of teeth, from their historical position as Schedule 2 products into Schedule 3.

  [Members recalled that the reference to "increased risk" was made when comparing the general exemption for pastes, powders or gels (≤ 1000 mg/kg) with that for other preparations, including mouth rinses (≤ 220 mg/kg). However, the October 2006

NDPSC Record of Reasons did not specify this and therefore did imply that the comment referred to pastes, powders and gels up to 2.5%.]

- XXXX proposed that the Committee consider either:
  - re-creating the separation between products containing > 1000 mg/kg fluoride ion for the cleaning of teeth and those for other applications; [Members noted that there was no such separation in the existing Schedule 3 entry, only in the Schedule 2 exemption]
  - align the wording for these products with the other exemptions to the Schedule 2 fluoride entry, underpinned by the RASML, through:
    - an additional clause in the Schedule 2 fluoride entry "(c) in preparations for topical use that are dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing more than 1000 mg/kg of fluoride ion but less than 2.5 per cent of fluoride ion, when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*";
    - a rewording of the Schedule 3 entry to "in topical preparations containing more than 1000 mg/kg of fluoride ion, but less than 2.5 per cent of fluoride ion, that are pastes powders or gels for use on teeth".

  XXXX asserted that this proposal removed the inconsistency, and limited the nature of the Schedule 2(c) category to dental hygiene, whitening or bleaching products that are pastes, powders or gels. XXXX asserted that the fluoride entry for RASML would only require a minor revision to capture these products. [Members noted some problems with the proposed wording and considered alternative wording that reflected XXXX intent i.e. pastes, powders or gels for use on teeth would be exempt from the requirements of scheduling when < 1000 mg/kg fluoride ion, Schedule 2 when 1000 mg/kg < fluoride ion ≤ 2.5%, and Schedule 3 > 2.5%.]
- XXXX acknowledged that the proposal moves to Schedule 2 dental hygiene pastes, powders and gels that are used for cleaning teeth that had historically been in Schedule 3, however the move was underpinned by the labelling safeguards afforded by RASML. [Members noted that no data was supplied to support the safety of this proposed down scheduling.]

Members also noted post-meeting comment from XXXX which asserted that there was need to reflect upon the Schedule 2 and Schedule 3 fluoride entries to address some specific anomalies and to confirm the intent of the wording of these entries. XXXX supported the above XXXX post-meeting comment.

The Committee also recalled the following from previous NDPSC Meetings:

<u>February 2004 NDPSC Meeting</u>

- Members considered dental hygiene products which were not dentrifices, such as mouth washes, containing 15 mg/kg < fluoride ≤ 220 mg/kg, including the possible

use of fluoride mouth washes by children and the concern that this could potentially lead to an increase in fluoride ingestion and the development of fluorosis. As the level of 220 mg/kg fluoride ion was still significantly lower than that in toothpaste the Committee considered that it was unlikely to pose any increased safety issues.

[Members noted that there appeared to be no consideration at this time of a possible inconsistency in that the exemption was reduced for mouth wash type products because of a probable increased risk, yet for 1000 mg/kg to 2.5 % fluoride ion these would be Schedule 2 when for the same range the 'less risky' pastes, powders or gels would be Schedule 3. A Member suggested that this may have been because all mouthwash type products at the time had <1000 mg/kg of fluoride ion.]

June 2004 NDPSC Meeting

- The Committee noted that the acute toxicity level given for accidental ingestion of sodium fluoride in children was 5 mg/kg fluoride. For a 10 kg child, this equated to ingestion of ~227 mL of mouthwash containing 220 mg/L fluoride. Members remained concerned at the risk of toxicity from ingestion of more concentrated fluoride products and agreed that CRC on these products should alert consumers to the potential toxicity as well as reinforce the message that such products were not appropriate for use in young children.

October 2006 NDPSC Meeting

- Members were advised that fluoride use in some whiteners was to deal with the temporary tooth sensitivity by remineralizing teeth. As such, these products did not appear to contain fluoride for the purpose of oral hygiene or preventing tooth decay and did not qualify for the TGA's oral hygiene Excluded Goods Order exemption. However, "dental bleaches or dental whiteners" were separately declared in the Excluded Goods Order (No.1 of 2005) not to be therapeutic goods, and this declaration did not limit itself to preparations not included in the SUSDP.
- Members considered a number of points from pre-meeting comments, including:
    - Advice that dental whitener product development and innovation in recent years had seen the addition of fluoride into some formulations at a level consistent with that used in cosmetic toothpastes (1000 ppm). It was noted that the SUSDP exempted toothpastes with this level of fluoride from scheduling.
- A Member asserted that the risk of the fluoride content in teeth bleachers and whiteners would be similar to existing non-whitening dental hygiene products i.e. toothpaste. The Committee agreed, noting that any separate concerns arising from the whitening active would be covered by the SUSDP entries for that active i.e. hydrogen peroxide. The Committee therefore agreed to align all fluoride containing bleaching and whitening formulations to the existing dental hygiene controls, not just pastes, powders or gels.

The Committee noted the following regarding the proposed cascade alternative (i.e. pastes, powders or gels for use on teeth would be exempt from the requirements of scheduling when < 1000 mg/kg fluoride ion, Schedule 2 when 1000 mg/kg < fluoride ion ≤ 2.5%, and Schedule 3 > 2.5%):

- A Member noted that pastes, powders or gels for use on teeth were exempt ≤ 1000 mg/kg and Schedule 3 at > 1000 mg/kg and asserted that with no Schedule 2 transition there was no real scheduling cascade.
- A Member asserted that the New Zealand pharmacy only classification only captured "cleaning of teeth". An alternative to the suggested cascade would therefore be to separate cleaning of teeth from non-cleaning of teeth in Schedule 3. Other Members noted however, that the New Zealand entry actually captured external use in medicines **other** than pastes, gels or powders for cleaning the teeth containing ≤ 2.5% (except in oral hygiene products other than pastes, gels or powders for cleaning the teeth containing ≤ 220 mg/kg and in packs containing not more than 120 mg of total fluoride; except in other medicines containing 15 mg/kg).
- A Member asserted that >1000 mg/kg pastes, powders or gels for cleaning of teeth would have higher chronic exposure than non teeth cleaning products. Other Members queried this assumption due to personal knowledge of people using non teeth cleaning products regularly and long term.
- A Member asserted that the Schedule 2/3 confusion discussed by XXXX was fully clarified by the October 2006 NDPSC decision, and that consideration of changing the Schedule 3 capture of such products would need to be supported by data. Another Member noted that the Committee had previously set the Schedule 3 cut-off to Schedule 2 due to safety concerns about long term use of high doses of fluoride, so any proposed change to the cut-off would require a revisiting of safety data. Indeed, a review of such data may provide good safety reasons for introducing a cascade.
- A Member recalled that while the original Committee consideration for setting the Schedule 3 cut-off was some time ago, it was considered intensively at several Meetings with a lot of data being presented. The Committee agreed that consideration of this cut-off should be undertaken in parallel with a revisiting of the fluoride risk assessment. The XXXX Member agreed that this could be provided for the June 2007 NDPSC Meeting.
- The Committee therefore agreed that, while confirming the October 2006 NDPSC decision, it would foreshadow consideration at the June 2007 NDPSC Meeting of the cut-offs in the fluoride entries, including the Schedule 3 cut-off.

Members also agreed that the foreshadowed consideration would include the possible inconsistency with the Schedule 2 cut-offs for mouth wash type products i.e. the exemption was reduced for these products (compared to paste type products) because of a probable increased risk, yet from 1000 mg/kg to 2.5 % these would be Schedule 2 yet the same concentration range of the 'less risky' pastes, powders or gels would be Schedule 3.

OUTCOME

The Committee agreed:

- to confirm the October 2006 NDPSC Decision (2006/48-13);
- to foreshadow consideration at the June 2007 NDPSC Meeting of the cut-offs in the fluoride entries including, but not limited to:
  - the Schedule 3 cut-off, particularly for non cleaning of teeth use patterns;
  - the possible inconsistency with the Schedule 2 cut-offs for mouth wash type products and whether there should be a cut-off to Schedule 3 for 1000 mg/kg to 2.5% fluoride ion.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

11.1 SEDATING ANTIHISTAMINES - BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DIPHENHYDRAMINE, DIPHENYLPYRALINE, DOXYLAMINE, PHENIRAMINE, PROMETHAZINE, TRIMEPRAZINE, TRIPROLIDINE

PURPOSE

The Committee considered the scheduling of sedating antihistamines as foreshadowed at the October 2006 NDPSC Meeting, including when in day-night packs and use in children < 2 years of age.

BACKGROUND

Day-night packs

Schedule 2 currently captures both the day and night components of day-night packs of most sedating antihistamines. The night formulation, while needing to be combined with one or more other therapeutically active substances, does not require a sympathomimetic decongestant. This includes solid or liquid preparations of brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine and triprolidine. However, this currently only applies to solid preparations of trimeprazine (all liquid preparations of trimeprazine are Schedule 3 or 4) and does not apply to diphenylpyraline or thenyldiamine (both only have Schedule 4 parent entries).

Children < 2

Most sedating antihistamines for use in children < 2 are currently Schedule 3 (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine and triprolidine). Only the diphenylpyraline and

thenyldiamine Schedule 4 entries capture all use in children < 2. The wording of the Schedule 2 and 3 trimeprazine entries allow some solid and liquid preparations to be available to children < 2 as Schedule 3 while capturing the remainder as Schedule 4.

General sedating antihistamines background

The October 2002 TTHWP Meeting recommended that New Zealand harmonise with Australia for antihistamine preparations combined with other active ingredients using the following broad principles:

- antihistamines and preparations with a significant potential for abuse be included in Schedule 4/Part 1;
- single-active preparations of sedating antihistamines be included in Schedule 3/Part II; and
- single-active preparations of non-sedating antihistamines and specified combination preparations of antihistamines be included in Schedule 2/Part III.

The February 2004 NDPSC Meeting amended the Schedule 2 entries for oral sedating antihistamines so that preparations for the treatment of symptoms of coughs, colds or influenza when combined with a sedating antihistamine were classified as Schedule 2 when at least one of the other therapeutically active substances was a sympathomimetic decongestant or when in a day-night pack containing the sedating antihistamine in the bed-time dose. Neither this Meeting or subsequent discussions on sedating antihistamines appeared to have considered the possibility of the day and night doses presenting in separate immediate containers despite being in the same outer pack.

The June 2005 NDPSC Meeting noted that the MCC agreed to harmonise on the scheduling of sedating antihistamines (except for mepyramine for which a separate recommendation had been proposed). Members confirmed that the scheduling of sedating antihistamines, amended at the February 2004 NDPSC Meeting, remained appropriate.

At the October 2005 NDPSC Meeting it was noted that there were combination sedating antihistamine products on the ARTG which contained a sympathomimetic (or phenylephrine with or without paracetamol) which were indicated for the treatment of conditions other than coughs, colds or flu. These products still fell within Schedule 3 even though they had addressed the concerns regarding sedation risk. The Committee therefore agreed to foreshadow an amendment to the sedating antihistamine Schedule 2 entries removing reference to indications and to allow all combination preparations containing a sympathomimetic decongestant to be considered Schedule 2 substances.

The February 2006 NDPSC Meeting agreed to the foreshadowed decision and also clarified the wording in relation to the age restriction “2 years of age or less” which

meant 2 years from the day of birth. This statement was replaced with "under two years of age" to avoid further misinterpretations.

The October 2006 NDPSC Meeting:

- Agreed to foreshadow an amendment to the Schedule 2 entries for some sedating antihistamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine, trimeprazine, triprolidine) which would restrict the inclusion of day-night packs by requiring that the day and night doses be in the same immediate container.
- Agreed to foreshadow requiring all sedating antihistamines for use in children < 2 to be Schedule 4.

DISCUSSION

Day-Night Packs

The Committee noted that various areas of the TGA were invited to comment on both the foreshadowed amendments. Members noted that responding advice included the following regarding the day-night packs issue:

- The draft minutes of the XXXX consideration of the foreshadowed amendments included:
  - There were a number of day-night products on the ARTG that contain a sedating antihistamine in the night dose. Many of these were included in Schedule 3 or 4 as they contain pseudoephedrine, while most of the rest were solid dose products.
  - The only currently registered liquid product affected by the proposal was XXXX currently Schedule 2. The only other registered liquid day-night sedating antihistamine product was Schedule 3 as it contained pseudoephedrine.
  - As the proposal would require inclusion of the day and night doses in the same immediate container, any solid dose day-night products with separate blister platforms for the day and night components would no longer be Schedule 2. The ARTG did not provide information on whether the day and night components were included in the same blister platform, and this information was not readily available, so any impact of the proposal on solid dose products was not clear.
  - XXXX commented that the proposal would have little effect on the availability of antihistamines in day-night products, and no effect on their abuse potential. It was suggested that the TGA should keep a watching brief on the issue.
  - XXXX had no objections to the proposed changes to the Schedule 2 entries for the sedating antihistamines [regarding day-night packs].

Members also noted the following pre-meeting comments regarding this issue:

XXXX:

- XXXX supported requiring day and night doses to be in the same immediate container but suggested it should also require that the content of night-time doses be proportional to day-time dose content. (Member's generally agreed that this was an issue for the regulator.)
- XXXX also contended that, if in the primary pack there are immediate containers which contain separate scheduled products (e.g. separate bottles for day and night doses, or separate tablet strips for day and night doses), the schedule of the complete package should reflect the highest schedule of the enclosed individual immediate containers.
- XXXX noted the definition of "immediate container" and "immediate wrapper" and questioned which applied to a foil strip as there were day-night packs which included separate day and night strips. XXXX suggested that unless day-night packs had a combination of day and night doses within the one strip, the schedule for the primary pack should reflect the highest schedule for the individual strips. [Members noted that the Therapeutic Goods Order 69 indicated that strip, blister and dial dispenser packs were "containers" and allowed an exemption from most labelling provided they were in a primary pack which was fully labelled. The SUSDP reflected this exemption by separating the definition of "immediate container" from "immediate wrapper" and requiring less labelling on immediate wrappers.]

XXXX:

- XXXX did not believe there was a need to differentiate between liquid and solid oral dose medicines. The important matter was to label bottles with clear and accurate dosage instructions. XXXX asserted that applying the principles of consumer-focused labelling and undertaking diagnostic testing to determine the effectiveness of the labelling (including the ease of distinguishing between the day and night formulations) should help resolve this matter.

XXXX:

- XXXX blieved that the proposal should not be adopted and that the current scheduling for sedating antihistamines should remain unchanged.
- XXXX advised the following regarding XXXX:
  - XXXX
- XXXX objected to the proposal for the following reasons:

  a) *There is no relevant evidence of abuse or misuse*:

  - No evidence was produced to the Committee of abuse or misuse of diphenhydramine products in combination with other therapeutically active substances, nor of multi-component day-night products. No evidence was produced that having the day/night dose in the same immediate container is relevant to the safety of day-night products.

- A summary of XXXX review of relevant literature and internal records noted that XXXX was not aware of any evidence:
  - of abuse of day-night products, despite the fact that a number have been on the market for some time as Pharmacy Only.
  - to support the proposal that day-night products should be scheduled according to whether the day/night doses are in the same immediate container.
  - to suggest that liquid-based day-night products should be scheduled differently to solid-based day-night products).

b) *The proposal is inconsistent with Trans-Tasman Harmonisation principles*:

- Until recently, Australian and New Zealand were harmonised regarding diphenhydramine. The Committee has foreshadowed adopting the new, more restrictive, New Zealand classification. XXXX believed this to be inconsistent with the principle of harmonising to the least restrictive schedule (giving due consideration to public health and safety issues and/or specific jurisdictional needs).

c) *The proposal is based on post-purchase separation of primary and secondary containers, rather than pre-purchase access to advice:*

- XXXX believed that the same controls on access should apply whether or not the day and night doses can, or will, be separated once the product has been purchased. The product concepts, indications, risks and benefits of day-night products, as well as pre-purchase advice, will be the same regardless of any potential for separation.
- Following purchase, where appropriate advice (if required) will have been provided, it becomes a function of the labelling to ensure safe and effective use by consumers.
- The proposal would allow more ready access to solid-based day-night products (which had less information on the primary pack e.g. blister strips) and would restrict access to liquid-based day-night products (which had more information on the primary pack). XXXX also noted that it was possible for some blister strips of tablets to be separated into their day and night components.

d) *The proposal is inconsistent with previous decisions regarding diphenhydramine*:

- It was asserted that a XXXX review of previous NDPSC decisions indicated that the current classification of diphenhydramine reflected the potential risks associated with the sedative effects of the antihistamine. XXXX suggested that whether a day-night product was liquid- or solid-based, the primary pack could be removed or the day/night components separated, the potential sedative risks would be the same.

e) *The proposal will inappropriately restrict access to safe and effective alternatives to solid dose day-night packs, which are especially important for children*:

- Numerous day-night products containing antihistamines in the bed-time dose are available in both Australia and New Zealand. XXXX believed that these day-night products were safe and effective when used according to label directions.
- Restricting access to liquid-based day-night products would make it more difficult for parents to obtain them and would limit treatment options for children who were over 2. The liquid product allowed the dose to be varied and was easier for children to swallow.

XXXX:

- Noted an interest in this item.

The Committee recalled the following from the October 2006 consideration of the day-night packs issue:

- The concern of both Medsafe and the MCC was that once the night-time dose containing diphenhydramine, when removed from the secondary container, it would be inappropriately classified on the primary container as a pharmacy-only medicine.
- The MCC felt that the product did not fulfil the intent of a pharmacy-only medicine and agreed that Medsafe should differentiate between day/night solid doses in the same platform and liquid day-night packs containing two primary containers, one of which contained a sedating antihistamine. [Members noted that it was unclear whether MCC considered the possibility of day and night solid doses contained in separate blister strips].
- A Member questioned whether it was fair to limit the formulation type to non-liquids, and asserted that perhaps labelling would be sufficient to distinguish the night-time formulation when it was not in the same immediate container as the day-time formulation.
- Another Member asserted that allowing night-time doses in the day-night packs to be Schedule 2 in the first place was a concession by the Committee when it was placing similar formulations in Schedule 3. This Member asserted that presently day-night products in which the doses were not in the same immediate container was pushing this concession too far.

Members generally agreed that there appeared to be a loophole in the current schedule wording that did not reflect the original intent of the Committee when it allowed day-night packs to be in Schedule 2 instead of Schedule 3. The Committee agreed to amend the Schedule 2 entries for sedating antihistamines in day-night packs to clarify the original intent.

Children < 2.

The MCC was asked to provide the data it took into account when considering sedating antihistamines for use < 2 at its June 2006 Meeting. Members noted the following provided in the XXXX response:

- A 2001 antihistamine report which touched briefly on the subject, including:

  Promethazine

  - A 1979 study reported on cases of SIDS and a possible association with medication including phenothiazines. The report noted that there was debate about a possible association of promethazine with SIDS. As the literature was limited, the report was unable to resolve this debate.
  - The report noted that it was common practice in New Zealand that children < 2 were given promethazine for night sedation and/or for cough in the belief that there are no known serious adverse effects. It was of concern that promethazine was easily available OTC and was also prescribed by GPs for infants without a warning. The report recommended that caution should be exercised when prescribing to infants and the datasheet should contain a warning about a possible association with SIDS.

  Trimeprazine

  - A 1985 study reported on 4 cases of an adverse cardiovascular response to oral trimeprazine as a premedication in children. Although none of the cases had a fatal outcome, all were characterised by bradycardia, hypotension and two required atropine and adrenaline infusion respectively.
  - The report noted that, as for promethazine, in New Zealand trimeprazine was given by parents to children < 2 as a night sedation or prior to travel in the belief that it had no serious adverse effects. The report asserted, however, that the literature supports the possibility of adverse cardiac effects. It was recommended that trimeprazine should be avoided in children < 2 and that the datasheet should contain a warning about potential adverse cardiac effects.

  Inappropriate use

  - This usually occurred with the aim of achieving paediatric sedation. The report noted a survey which found that, beyond the two recognised indications (symptoms of cold/flu and allergic conditions), a sedating antihistamine was administered in 16% of cases because the child has difficulty sleeping and in further 16% of cases because the mother herself was not coping. This rose to 32% if the age group was ≤ 2. Also noted was that 12% of GPs prescribed antihistamines for child sedation and that only 30% of mothers read OTC medicine labels to find out whether they were suitable for children.

  Conclusion

- There was an issue with antihistamine preparations being used as a sedative in young children. Consideration should be given to the suggestion that antihistamines that are likely to be used in children < 2 should carry warnings about the possibility of serious adverse effects. Unfortunately there was limited data in this area but the possibility that these medicines may increase the risk of SIDS in infants cannot be excluded.

- XXXX advised that the only other document considered was an FDA alert warning about the potential for fatal respiratory depression with promethazine in children < 2.
- The MCC rationale was that until there was evidence to show that other medicines in this class were not associated with this adverse event, the whole class should be treated in the same way as promethazine. XXXX. It was apparent that the MCC Members had thought about this prior to the Meeting and were unanimous in their view that sedating antihistamines should be prescription medicines for children < 2.

As noted above various areas of the XXXX were invited to comment on both the foreshadowed amendments. Advice was subsequently received and included the following regarding the children < 2 issue:

- XXXX advice regarding:
  - The MEC guidelines, noting that the section on 'paediatric products containing antihistamines' (Chapter 9 of the current ARGOM) - states:

    Paediatric products containing antihistamines

    The dosage instructions for paediatric products containing antihistamines labelled for use in children under 2 years of age should advise (at the beginning of the directions for use in this age group) that the product is only to be given in this age group following the advice of a health care professional (see also Paediatric cold and flu products below). Where the product is indicated for sedation in children up to the age of 12 years, the label should also advise (at the beginning of the directions for use in this age group) that the product is only to be given in this age group following the advice of a health care professional.

    The labels of paediatric products containing promethazine should advise (at the beginning of the directions for use) that they should not be used in children under 12 months of age and that the advice of a doctor should be sought before administering the product to children from 12 to 24 months of age. A dose for children in the 12 to 24 month age group need not be included on the label where the product has a TGA approved published Product Information (PI) that the doctor can refer to in determining the correct dose. Where there is no PI and no dose on the label, the label must include a statement such as "Not recommended for use in children under 2 years".
  - Advice on the question of whether any sedating antihistamines are indicated for use < 2 and whether these products carry warnings against use in this age group. This advice included the following (noting that the situation was sometimes unclear as these substances were often used in combination and, therefore, the specific indications and references to children could be influenced by the presence of other substances):

- Some products containing diphenhydramine and brompheniramine were indicated for use under 2 years of age only on the advice of a doctor or pharmacist. A dexchlorpheniramine product included the indication that it was not to be given to children less than 1 without medical advice.
- A chlorpheniramine product included an indication for use for 1-2 years. A promethazine product and a trimeprazine product had the indication not to be given to children under 2. A doxylamine product had the indication do not give to children under 12.
- Pheniramine – no indications found for children under 2. Triprolidine – unclear. No products were located on the ARTG containing diphenylpyraline or thenyldiamine.

Members also noted that the following pre-meeting comments regarding this issue:

XXXX:

- XXXX did not support the proposal without the provision of more evidence of the risk and harm of these products, as a complete class, to this particular patient group. XXXX proposed that if a causal link between these products and infant mortality or morbidity was identified, future consideration should be for individual medicines rather than as a general class.
- The proposed change would affect a wide range of medicines, including single-ingredient products such as dexchlorpheniramine syrups used for indications such as allergic reactions, sedation or anti-emesis. Also affected were some combination products marketed for cough, cold and flu symptoms, such as chlorpheniramine + phenylephrine, brompheniramine + phenylephrine and brompheniramine + phenylephrine + dextromethorphan.
- XXXX noted MCC's concerns that sedating antihistamines had been implicated in sudden death in children < 2 and that there was anecdotal and published evidence of misuse and abuse in children. XXXX had only been able to find concern being expressed about the phenothiazine antihistamines (promethazine and trimeprazine) and a possible relationship to infant sleep apnoea and SIDS, and this concern had mostly been recommending more assessment to further determine if there was a causal link. XXXX was unable to find any reference of concern for alkylamine antihistamines such as chlorpheniramine, dexchlorpheniramine and brompheniramine. XXXX therefore had concerns that the class consideration may be unnecessarily restricting safe and efficacious products.
- XXXX noted that restricting to Schedule 4 will restrict consumer access and increase the costs. XXXX also had concerns that, in an effort to avoid paying such additional costs, parents may resort to purchasing the non-prescription syrups aimed at older children and guessing doses for the age groups not included on the container. This

would have a greater risk of ill-effects from overdosing. Pharmacists who provided dose advice could also be professionally compromised.

- XXXX was also interested to know whether the anecdotal and published misuse and abuse evidence reported at the October 2006 NDPSC Meeting [*referenced by MCC material*] detailed whether this was from improper supply on professional recommendation or whether it was improper use contrary to the professional advice. [Members noted that the advice from MCC did not give this level of detail, although the 2001 report did broadly mention use by parents both with, and without, professional advice.]

XXXX:

- XXXX did not support the proposal, particularly with regard to chlorpheniramine and dexchlorpheniramine. XXXX advised that it is the sponsor of XXXX
- The scheduling for chlorpheniramine, dexchlorpheniramine and promethazine in a number of countries was presented. All these countries classified chlorpheniramine and dexchlorpheniramine as OTC medicines. With regards to promethazine, some countries classified this as OTC whilst others classified promethazine as a Prescription Medicine.
- XXXX supplied details of the indications for XXXX, noting that these were relatively non-serious conditions readily treatable without medical intervention but can cause considerable distress for a child. Some conditions, e.g. insect bites, need easy access to antihistamines to allow prompt relief. Additionally, for some conditions, the sedating effect may be a useful adjunct to the antihistaminic actions.
- XXXX asserted that whilst there may be misuse and abuse concerns, the major impact of the proposal would be to limit access to safe, effective medicines by consumers who use them appropriately. The inconvenience/distress associated with treatment delay due to the need to obtain a prescription would be increased. XXXX also reiterated XXXX costs argument.
- XXXX also noted the requirement for a pharmacist to be involved in the supply of Schedule 3 products i.e. could provide advice regarding correct use (including age suitability) as well as identifying situations where potential for abuse exists.
- XXXX discussed the following regarding MCC's 2006 review of this issue:
    - Regarding the MCC's reference to 'some sedating antihistamines' being implicated in sudden death in children < 2, XXXX advised that it reviewed ADRAC reports (back to 1960) in relation to XXXX, where causality was assigned as being 'possible' or greater. No reports of sudden death were identified. XXXX was also unaware of any reports that associated chlorpheniramine or dexchlorpheniramine to sudden death in children < 2.
    - Though there has been debate associating promethazine with SIDS, the literature in this regard had been claimed to be 'rather limited'. However, XXXX did note

the FDA promethazine report discussed above. XXXX noted that while MCC raised concerns in relation to a possible SIDS association for promethazine, no such concerns were raised for chlorpheniramine or dexchlorpheniramine.

- Regarding the MCC's reference to 'anecdotal and published evidence of misuse and abuse of these medicines in children', XXXX advised that in the above review of ADRAC data, no reports were identified where XXXX might have been used inappropriately in children aged < 2. In older children, 3 reports were identified that could potentially be classified as cases of inappropriate use (although little information was available).
- In addition, XXXX noted MCC reference to the 2001 antihistamine report and observed that the report concluded that chlorpheniramine was generally regarded to be one of the less sedating first generation H1 antagonists.

- XXXX therefore concluded that, in the absence of evidence linking chlorpheniramine and dexchlorpheniramine with increased incidence of side effects in children < 2, Schedule 3 was an appropriate balance between access and caution with sedating antihistamines for this age group.

XXXX late additional comment:

- Additional comment was received from XXXX after the pre-meeting comment deadline. Members agreed to use their discretion and allow consideration, noting:
  - The cumulative search of the global XXXX pharmacovigilance database was performed for serious adverse events in neonatal or paediatric patients < 2. Reports of sudden death, or reports of misuse, abuse or inappropriate use which would have resulted in a serious adverse event, would all be captured in this query. In all, twelve reports were identified. XXXX asserted that these reports needed to be considered within the context of the long history of safe use of products containing sedating antihistamines. Details of the reports were provided by XXXX.

XXXX:

- XXXX was concerned that the Committee was considering this issue without adequate evidence that could justify the rescheduling. XXXX asserted that potential for abuse was only one criterion for a scheduling consideration and that this must be balanced by considering other factors including benefits.
- In Australia, sedating antihistamines have been available both for use in children and adults for decades with very few adverse event reports to ADRAC. Products that include dosage instructions for children < 2 were indicated for symptoms of upper respiratory conditions and allergies/insect bites, not sedation. Further, as far as XXXX could determine, all except one include a sedating antihistamine in combination with phenylephrine, believed to counter the sedating effects of the antihistamine.

- The October 2006 Record of Reasons included information on adverse event reports following use of promethazine in children < 2. XXXX noted that medicines containing promethazine were approved for use as a sedative for short-term use, but only for children > 2. The PI for these medicines clearly advised they are not to be used in children < 2.
- XXXX reiterated XXXX observation regarding pharmacist involvement in supply, and XXXX concern about rescheduling encouraging misuse of non-prescription products indicated for other age groups.
- Assuming the accuracy of anecdotal evidence about misuse, XXXX was not convinced that rescheduling of these medicines would help resolve the matter, as reducing access did not necessarily equate to a reduction in misuse/abuse.
- XXXX put forward two options:
    - XXXX preferred position was to maintain the current scheduling regime for these medicines.
    - A second option was to maintain non-prescription status, but remove the label dosage instructions for children < 2, and add a statement to the effect that a pharmacist or doctor must be consulted to determine if appropriate for children < 2.

  For either of these options, sponsors would be required to retain PI and CMI. All dosage instructions could be included in the PI for use of pharmacists and doctors, with the CMI providing the same information as the label, i.e. the need for a health professional to advise if suitable for a child < 2 and, if so, the appropriate dose.

XXXX:

- Further information was needed before all sedating antihistamines could be rescheduled to Schedule 4 (when indicated for children < 2 years of age). The proposal failed to take into account the characteristics and safety profiles of the different substances (e.g. sedative and other adverse effects, possibility of respiratory depression, or evidence of misuse). XXXX opposed applying one decision to the whole class.
- While some sedating antihistamines have been implicated in sudden infant death, XXXX believed more information on all of these substances was needed considering the number of products on the market and the range of indications they have.

XXXX:

- While these comments supported the proposal "to place all sedating antihistamines in Schedule 4 when intended for use in children < 2" for the phenothiazine antihistamines, notably promethazine and trimeprazine, they did not support the proposal for other first generation antihistamines without more specific data.

XXXX:

- Noted an interest in this item.

A Member requested that a January 2007 article from the CDC on the use of cough and cold preparations in infants be provided for consideration by the Committee (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm). Members noted, however, that the article was primarily concerned with pseudoephedrine overdose, and the dangers to infants of cumulative doses from multiple medications.

The Committee recalled the following from the October 2006 NDPSC consideration of the children < 2 issue:

- The June 2006 MCC Meeting noted its earlier concern that sedating antihistamines were available over the counter for children < 2. MCC noted that some sedating antihistamines had been implicated in sudden death in this age group. There was also anecdotal and published evidence of misuse and abuse of these medicines in children. MCC was unanimously of the view that sedating antihistamines should be used in this age group only under medical supervision.
- The Committee noted that the proposed change to the scheduling of sedating antihistamines would impact on a range of products in the marketplace. It was also noted that despite many years of use, there had been no adverse incidents reported which might suggest that the current scheduling was not appropriate. Changes to scheduling without adequate evidence was undesirable. Another Member noted, however, that reports of adverse events in regard to the use of promethazine, including reports of death, had only come to light in the last two years.

A Member asserted that the case for restricting these products for children < 2 to Schedule 4 was stronger for the phenothiazine antihistamines, notably promethazine and trimeprazine. There did not appear to be much evidence for the remaining sedating antihistamines. The Member noted, however, that no data did not mean 'no risk', and perhaps the Committee should consider a precautionary approach to the class.

A Member also noted that the view of XXXX was shaped by a different standard of evidence than those areas assessing efficacy as XXXX dealt with XXXX that often had little high quality data. In this case such an approach would tend to support extrapolating the promethazine and trimeprazine evidence to the whole class of sedating antihistamines for use in children < 2 unless data was presented to support the contrary. Another Member noted that it was a characteristic of most medicines, including sedating antihistamines, that there was insufficient evidence on safety (and efficacy) in this population of patients.

A Member noted that the FDA data included some serious flags (including deaths), although the risk from the whole class was indeterminate. Another Member noted that no FDA approved dosing recommendations existed for administering OTC cough or cold medications to children, although it was also noted that such products would include combination and pseudoephedrine products.

A Member also noted recent personal accounts from New Zealand (where any of these products with instructions for use < 2 are to become Prescription medicines) of parents being denied product for their < 2 infant returning later to obtain the product for their "older child". Another Member agreed that there are practical problems when scheduling for an age group that the regulator would need to consider.

The Committee generally agreed that it needed more information before it could change the scheduling of sedating antihistamines for use in children (particularly those < 2) and that advice would be sought from XXXX and XXXX to aid a consideration at the June 2007 NDPSC Meeting. XXXX would specifically be asked about XXXX view on:

- evidence around the side effect profile of sedating antihistamines for use in children;
- whether there were differential degrees of evidence for different products/substances and whether any risks applied across the class;
- how the above applied specifically for children < 2 and children < 12.

Additional Unharmonised Sedating Antihistamines

Members recalled that the October 2006 NDPSC Meeting noted that there had been an error with the diphenylpyraline scheduling and agreed that the diphenylpyraline amendment in SUSDP 21 Amendment 1 (part of decision 2006/47-5) was not valid. The Members therefore agreed to delete this entry in SUSDP 21 Amendment 2 i.e. diphenylpyraline was only captured by the Schedule 4 parent entry. XXXX advised that harmonisation with the diphenylpyraline Schedule 4 entry was now in hand and would take place following the next MCC Meeting.

OUTCOME

Children Under 2

The Committee agreed to foreshadow consideration of the scheduling status of sedating antihistamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, diphenylpyraline, doxylamine, pheniramine, promethazine, thenyldiamine, trimeprazine and triprolidine) for children at the June 2007 NDPSC Meeting., particularly children under two years of age.

DECISION 2007/49 – 16

Day-Night Packs

The Committee:

- noted that there was a risk, when using day-night packs containing sedating antihistamines in which the day and night formulations were in separate immediate containers or immediate wrappers, of inadvertent use of the night formulation

(without a sympathomimetic decongestant) in the day and being unaware of the possibility of sedation; and

- agreed to the foreshadowed amendments to the Schedule 2 entries for some sedating antihistamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine, trimeprazine and triprolidine) which will clarify the Committee's original intent by restricting the inclusion of day-night packs by requiring that the day and night doses are in the same immediate container or immediate wrapper.

Schedule 2 - Amendments

BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DOXYLAMINE, TRIPROLIDINE – Amend entries to read:

[SUBSTANCE] when combined with one or more other therapeutically active substances in oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing [substance] in the bed-time dose where the day and night doses are in the same immediate container or immediate wrapper,

except in preparations for the treatment of children under 2 years of age.

DIPHENHYDRAMINE, PROMETHAZINE - Amend entries to read:

[SUBSTANCE] in oral preparations:

(a) in a primary pack containing ten dosage units or less, for the prevention or treatment of motion sickness; or

(b) when combined with one or more other therapeutically active substances when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing [substance] in the bed-time dose where the day and night doses are in the same immediate container or immediate wrapper,

except in preparations for the treatment of children under 2 years of age.

PHENIRAMINE – Amend entry to read:

PHENIRAMINE:

(a) in eye drops; or

(b) when combined with one or more other therapeutically active substances in oral preparations when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing pheniramine in the bed-time dose where the day and night doses are in the same immediate container or immediate wrapper,

except in preparations for the treatment of children under 2 years of age.

TRIMEPRAZINE – Amend entry to read:

TRIMEPRAZINE when combined with one or more other therapeutically active substances in solid oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing trimeprazine in the bed-time dose where the day and night doses are in the same immediate container or immediate wrapper,

except in preparations for the treatment of children under 2 years of age.

11.2 PANTOPRAZOLE

PURPOSE

The Committee noted the inclusion of pantoprazole as a standing item on the agenda to remind the Committee that the implementation date for the June 2005 Decision, to include an entry in Schedule 3 for pantoprazole, was 1 May 2008.

11.3 ORLISTAT

PURPOSE

The Committee considered the current scheduling and Appendix H listing of orlistat.

BACKGROUND

Orlistat is a potent, specific and reversible long-acting inhibitor of gastrointestinal lipases which are required for the systemic absorption of dietary triglycerides. It is used in conjunction with dietary modification and physical exercise in the management of obesity.

Orlistat was first considered at the November 1999 NDPSC Meeting, when it was included in Schedule 4 (S4) following a recommendation by the trans-Tasman Harmonisation Working Party. The May 2000 NDPSC Meeting noted that the ADEC, at its December 1999 meeting, recommended the registration of XXXX capsules containing orlistat 120 mg for the treatment of obese patients with a body mass index (BMI) > 30, and overweight patients with a BMI > 27 in the presence of other risk factors, in conjunction with a mildly hypocaloric diet.

Separate submissions to reschedule orlistat for the treatment of obesity from S4 to S3 were considered at both the June 2002 and February 2003 NDPSC meetings. The February 2003 submission also sought to have orlistat included in Appendix H. On both these occasions, the Committee decided that the information submitted by the sponsor did not provide adequate evidence to address the Committee's concerns in relation to its safety profile; to the necessity for medical assessment to determine a patient's suitability for treatment with orlistat; and to the view that therapeutic intervention should not be the first-line treatment for obesity.

The October 2003 NDPSC meeting considered a third new submission to reschedule orlistat for the treatment of obesity from S4 to S3 without inclusion in Appendix H. The NDPSC agreed to reschedule orlistat from S4 to S3 for the treatment of obesity on the basis that the sponsor had provided adequate evidence addressing the Committee's previous concerns.

Both the February 2005 and June 2005 NDPSC Meetings considered two separate proposals to include orlistat in Appendix H of the SUSDP. The Committee did not support the proposal as members were concerned that omission of information in advertising campaigns about the modest efficacy and reduction of efficacy long-term seen in the clinical trial setting and potential side effects of orlistat might create a consumer demand based on unrealistic expectations of the product's effectiveness. Furthermore, the Committee remained concerned that branded advertising of orlistat would convey an inappropriate public health message that pharmacotherapy is the first-line treatment for obesity. The Committee was also of the view that branded advertising would make

consumers less likely to be influenced by the pharmacist's assessment in determining whether the product is suitable for them. The Committee reaffirmed its position that consumers should be encouraged to undertake appropriate lifestyle changes as a first-line option to achieve safe, long-term weight loss.

At the February 2006 NDPSC Meeting, the Committee considered a new application from XXXX. The Committee noted additional information on a post-marketing surveillance study, media survey and consumer/market research, as well as the experience gained by pharmacists in screening and consulting patients on the suitability of orlistat for other conditions. The Committee also believed that the newly amended Therapeutic Goods Advertising Code (TGAC), which had been strengthened with regards to the advertising of weight loss products, would ensure responsible and appropriate banded advertising of orlistat by the sponsor. The Committee hence agreed to include orlistat in Appendix H on the grounds of potential public health benefit (Decision 2006/46-29). This decision was confirmed at the June 2006 Meeting.

At the October 2006 NDPSC Meeting, the Committee considered the media attention which had been focused on the direct-to-consumer advertising of orlistat particularly during the television program *Australian Idol*. At this time the Committee also considered a submission from XXXX which requested the Committee review the scheduling and Appendix H listing of orlistat. After discussion of these issues the Committee agreed to foreshadow consideration of the scheduling and Appendix H listing of orlistat for the February 2007 Meeting.

DISCUSSION

The Committee recalled the following matters from the October 2006 NDPSC meeting:

- In 2004 XXXX publicly criticised the decision to make orlistat for weight control purposes available on the professional advice of a pharmacist claiming that it would potentially lead to use by inappropriate patients and the likely abuse of the product. XXXX raised concerns about the safety of orlistat and considered that the wider availability of orlistat as a Pharmacist Only Medicine would impart the wrong public health message. It was then XXXX view that orlistat for the treatment of obesity should be available only under the supervision of a medical practitioner in order to ensure it is used appropriately. The NDPSC decided the initial (2004) concerns raised by XXXX could be addressed adequately through the Product Information, Consumer Medicine Information and appropriate labelling. Additionally, pharmacists must comply with professional standards and codes of practice which require medicines to be supplied appropriately.
- There had been media coverage on the advertising of orlistat particularly during the television programme *Australian Idol*. Both XXXX had criticised the advertising of orlistat during prime time TV. XXXX had stated that advertising orlistat direct to consumers gives a misleading message and that it is a medication that shouldn't be

allowed to be advertised direct to consumer. XXXX had also commented that the decision to allow direct to consumer advertising needs to be reviewed, as must the decision allowing orlistat to be available without prescription. XXXX believed that the advertising campaign is in breach of the TGAC. Their argument was that the code prohibits the advertising of pharmaceuticals to people under the age of 18 and the core audience for the *Australian Idol* program is girls in the 13-17 year age group. XXXX also expressed concern that the advertisements for orlistat send the message to young women that taking a pill is a solution to weight problems rather than undertaking a balanced diet and exercise regimen.

- The Committee noted that XXXX had written to the Chair asking that the Committee reconsider the scheduling and Appendix H listing for orlistat. XXXX requested that advertising approval be revoked immediately and that orlistat be rescheduled to Schedule 4.
- XXXX.

The Committee noted the following information obtained from the public TGACC website *(http://www.tgacc.com.au/complaintSingle.cfm?id=731)*. The CRP (the Panel) heard the complaint made by Choice against Roche's advertising of Xenical during Australian Idol on 19 October 2006. Choice's complaint made the following allegations;- (a) the TVC targets anyone who may think they have a weight problem, not just the population it is indicated for, (b) the advertisement was in breach of section 4(2)(f) of the Therapeutic Goods Advertising Code (the Code), (c) the advertisement was also in breach of section 4(2)(j) of the Code and (d) That the advertisement fosters the idea that a pill is the cure for obesity, which amounts to sending an inappropriate message to consumers. Choice also suggested that the success of this advertising campaign may encourage other manufacturers to apply for rescheduling of their products which may ultimately result in consumers being bombarded with advertisements for a wider group of drugs not currently advertised. Roche provided a response to the CRP which encompassed the same points as it made in its response to the TGA (see above) as well as the contention that the TVC did not foster any impression that a pill is a cure for obesity. Roche also addressed the concern of Choice over the potential rescheduling and advertising of other products by stating the the rescheduling process is very difficult and that the Xenical TVC does nothing more than alert consumers to the availability of an evidenced based product they need to ask their pharmacist about. The CRP made the following points and recommendations:

- The Panel reviewed the demographic and ratings data provided by Roche and formed the view that the advertising schedule did not appear to be directed to minors. Many advertisements could be incidentally viewed by minors but this would not be sufficient to bring the advertisement within the scope of section 4(1)(j). The Panel also viewed the advertisement and noted that it did not differ from that which had been approved by ASMI. The panel were unable to discern any signs that it was directed at minors and thus considered it was not in breach of section 4(1)(j) of the Code.

- In viewing the advertisement, the Panel considered the spoken words and superimposed text used relating to using the product in conjunction with diet and exercise were sufficient to meet the requirements of section 7(3) of the Code (which states that advertisements for weight management products must have an appropriate balance between the claims and references to healthy diet and physical activity.) The Panel also noted that the words appeared in the advertisement for a lengthy period of time.
- The Panel considered the indications of the product and noted they are highly specific in regards to appropriate consumers of the product. Section 22(5) of the Therapeutic Goods Act (the Act) states that therapeutic goods must not be advertised for an indication other those which are included in the Australian Register of Therapeutic Goods (ARTG). The Panel considered that the advertisement was in breach of this part of the Act as well as Section 4(2)(f) of the Code as it does not state the BMI requirement for access to the substance and this fact needs to be clarified because many of the viewers of the advertisement were not appropriate candidates for supply of the product.
- In reaching this conclusion the Panel also noted that Roche made several references to the intervention of a pharmacist in supply of the product which they believed would stop inappropriate access to the product. While the Panel accepted this would likely be the case, it did not accept that the existence of such a process would affect the interpretation of the advertisement by consumers and noted that all advertisers must be aware of section 3(2) of the Code which states that the conformity of an advertisement with the Code should be assessed in terms of its probable impact upon the reasonable person to whom the advertisement is directed.
- In making the above decision the Panel did not form a view as to whether specific references to BMI or other technical data would be necessary. Rather, the Panel was mainly concerned about the lack of qualification of the phrases used in the advertisement. These phrases, in the Panels' view, implied that any person wishing to lose weight could be supplied with the product.
- Given this decision the Panel requested that Roche Products Pty Ltd, in accordance with sub regulation 42ZCAI(1) of the Therapeutic Goods Regulations 1990 (the Regulations):

  (a) withdraw the advertisement from further broadcast;

  (b) withdraw the unqualified representation that the product is suitable for anyone wishing to lose weight;

  (c) not use such a representation unless Roche satisfies the Panel that it would not constitute a contravention of the Act, Regulations or Code;

  (d) provide the Panel with evidence of compliance to the above requests within 14 days.

- The Panel also noted that Roche should be aware that the Panel, under sub-regulations 42ZCAI(3) and (4), may recommend to the Secretary that in the event of non-compliance with these sanctions, the product be cancelled from the ARTG.

There had been various media reports (News.com.au on 21 November 2006 and Pharmacy Review in its December 2006/ January 2007 edition) covering the withdrawal of the TVC XXXX. There had also been widespread coverage, both in print and visual media, in the lead up to the Meeting of the NDPSC's consideration of the issue.

XXXX ran a consumer email campaign directing consumers to the NDPSC Secretariat and requesting that orlistat be immediately removed from Appendix H and that the substance be returned to Schedule 4 of the SUSDP. The NDPSC Secretariat had received 36 of these emails. XXXX had also provided a submission in which XXXX opposed the continued Schedule 3 and Appendix H listing for orlistat. XXXX main points were:

- In late 2006 XXXX heard anecdotal evidence from pharmacists that girls as young as 13 in the healthy weight range were asking for orlistat. This was the trigger which led XXXX to conduct a shadow shop of 30 pharmacies in the Sydney Metro area to determine:
  - if people with a BMI of less than 30 with no risk factors were sold orlistat by pharmacies;
  - if pharmacies were following the procedures developed by the Pharmaceutical Society of Australia (PSA).
- The shopper completed a questionnaire which consisted of 24 questions at the end of each transaction. The purpose was to record her experience at each pharmacy so data could be collated about how the drug was dispensed and if pharmacists were following the PSA guidelines. She filled in a questionnaire immediately after leaving each pharmacy.
- The shadow shopper was a 19 year old female full time student with a BMI of 25 and no co-morbidities. She had never used orlistat. Her BMI was verified by XXXX laboratory staff on the first day of her shadow shop in December 2006.
- XXXX found that 80% of the pharmacies sold the product to the shadow shopper, even though she did not meet the criteria for the drug. XXXX also found that few pharmacies were following the guidelines developed by the PSA by failing to confirm whether orlistat was suitable for the customer (by not checking height (100%), weight (96%) or calculating her BMI (92%)) and not counselling the patient on lifestyle changes. None of the consultations took place in a private area and not all pharmacies advised her of side effects of the substance. The shadow shopper also noted that the substance was sold to her by a pharmacy assistant on at least one occasion and that it was often difficult to determine if the product was sold to her by the pharmacist or an assistant as badges were not worn.

- The shopper also noted comments from pharmacists such as "although she doubted I was obese that it's good to set a target weight goal to aim for" and "he said that I didn't really look like I needed to lose weight, so I could probably use it for around two months". In total there were 3 cases where the pharmacist stated the shopper did not need the drug but sold it to her regardless, indeed one pharmacist who calculated the shoppers' BMI as 25 sold her the product.
- XXXX stated that in a busy retail environment, the pharmacist may not always have time to undertake a proper consultation. Indeed, the average consultation time was 6.2 minutes, with some pharmacists undertaking no consultation at all.
- As orlistat is an S3 drug, it is up to the ethics of the individual pharmacist to determine whether or not to sell the drug to a consumer who does not meet the clinical criteria. While some pharmacists will not sell the drug if it is not appropriate, the shadow shop revealed that a significant majority dispensed the drug even though the consumer did not meet the guidelines for the drug.
- XXXX also noted that it was now possible to buy orlistat from online pharmacies and, while the consumer must talk to the pharmacist over the phone, the pharmacist does not see the consumer, and therefore cannot measure their BMI. XXXX stated that returning orlistat to Schedule 4 status will solve these problems as the patient will need to see their doctor in person in order to obtain a prescription. The Committee understood that the supply of S3 medications through an online pharmacy requires a prescription.
- With regard to the advertising of orlistat, XXXX stated that the marketing strategies employed by XXXX encourage excessive use of the substance and that the CRP found them in breach of the section of the Code (4(2)f) which covers this. XXXX also noted that the CRP found XXXX in breach of section 22(5) of the *Therapeutic Goods Act 1989* which states that a sponsor must not advertise goods for any indication other than that which they are registered for.
- XXXX argued that while these advertisements were withdrawn, the fact that orlistat is in Appendix H means that XXXX can advertise the drug in the future. While the withdrawn advertisements may not be used again, there is no guarantee that future advertising will not inadvertently stimulate demand in consumers who do not have the appropriate indication; indeed it is hard to imagine an advertising campaign which would not do so.
- XXXX stated that the NDPSC will need to consider that the purpose of an advertisement is to encourage use and whether there is a public health detriment from allowing orlistat to be available as an S3 substance.
- XXXX also felt that XXXX had adopted a novel marketing strategy by seeking to schedule orlistat to S3. By doing so they were circumventing the prohibitions against direct to consumer advertising and are thus able to reach a much larger audience. The Committee noted that the advertising of S3 substances included in Appendix H is not prohibited. XXXX stated that the marketing strategies employed for this campaign

have been very clever. The 'X Plan' (a telephone advice line for consumers who purchase the drug and which the packaging of the substance encourages patients to join) gives the impression that the questions that call centre workers ask are (their doctors name, where the product was bought, whether they have a healthcare card, their current weight etc) for the benefit of the consumer, when in fact the answers provide XXXX with marketing data, and this appears to be their primary purpose.

- XXXX noted that the NDPSC had concerns regarding its rescheduling of orlistat, including the safety profile of the drug not meeting S3 requirements, that the assessment of a medical practitioner was required to determine suitability and that it would give the public the incorrect perception that it was a first line treatment for obesity.
- XXXX suggested that subsequent events, including the inappropriate advertising of the substance and the results of the shadow shopper suggest that the NDPSC was right to be concerned about rescheduling orlistat to S3. XXXX noted that one of the main reasons orlistat was rescheduled was the belief that pharmacists could provide good advice to consumers, identify co-morbidities and monitor the misuse of orlistat. The XXXX shadow shopper had found however, that pharmacists are generally not following the guidelines and indeed, that the majority are dispensing the drug inappropriately.
- The submission by XXXX then addressed each of the individual criteria under S 52E of the *Therapeutic Goods Act 1989* which the NDPSC must consider when making a determination with regard to why orlistat should be made a Schedule 4 substance:

  (a) Long term safety of the substance has not been established and there were several risks in using orlistat long term including decreased absorption of fat-soluble vitamins and an increase in macular degeneration.

  (b) There is a lack of information on the long-term risks of the substance, though there is information on the benefits of its use. However these benefits only accrue to consumers who meet the clinical profile. Evidence including that set out above suggests that it is not possible to limit distribution of orlistat to the appropriate target group while it is listed as a Schedule 3 drug.

  (c) The mainly gastrointestinal side effects are unpleasant and could potentially lead to more serious conditions if intake of the drug is not ceased. Therefore it is desirable for these reasons, that the use of the drug be monitored by a medical practitioner.

  (d) Data on all obesity drugs including orlistat is "limited by modest efficacy and low rates of persistence with treatment" and the NPS notes that orlistat will not help all patients achieve successful weight loss, especially if there are no accompanying lifestyle changes.

  (e) XXXX stated that XXXX do not have expertise to comment on the dosage or formulation of the substance.

(f) Orlistat should be available to consumers in Australia, however not as a first line therapy. Diet, exercise and behavioural therapy should be used in the first instance.

(g) Some young women may be particularly vulnerable to manipulation based on concerns about body image. Therefore there is great potential for the substance to be abused. This threat would be markedly reduced if it was scheduled to S4.

(h) The substance is only suitable for consumers with a BMI over 30 or 27 if there are co-morbidities. However, it is being sought by, and made available to, people in the healthy weight range.

- XXXX concluded that evidence showed that orlistat was being dispensed inappropriately and that marketing messages have helped facilitate this. XXXX also stated that pharmacists are not in a position to ensure that only appropriate customers were dispensed the substance. Rescheduling orlistat to S4 would ensure that it was only dispensed to consumers who have been counselled by their GP and who meet the clinical criteria and pharmacists would not be able to sell the drug to consumers who did not meet the clinical profile for the drug. This would relieve pharmacists of the temptation to sell the drug to consumers with a BMI under 30.

XXXX provided a pre-meeting submission stating that it was in the interest of public health that orlistat remain accessible through pharmacies and that direct to consumer advertising gives the greatest opportunity for the most appropriate patients to be guided by pharmacists. XXXX main points were:

- All of the previous reasons that the NDPSC considered appropriate for the down-scheduling of orlistat in October 2003 remain current in January 2007 (i.e., the safety profile of the substance, that it is reasonably efficacious, obesity is a disease easily recognised by consumers, pharmacists have good training and experience in providing advice on this issue, orlistat has a low abuse potential.)
- XXXX believed that, as obesity is still a critical national health issue, it is not in the public health interest to reschedule the substance to S4 as there are many consumers who have benefited from orlistat being made more accessible. XXXX acknowledged that orlistat is not a cure for obesity, however even the benefits of moderate weight loss are well documented. XXXX also stated that the rescheduling of orlistat to S4 will lead to a reduction in the educational and supportive work carried out by pharmacists and to the detriment of the XXXX patient support program and that both of these outcomes would not serve the interests of public health.
- XXXX stated that many consumers visit pharmacies each day and ask pharmacists for their advice on health issues. XXXX noted that these pharmacists receive ongoing education and training with regards to counselling patients about weight loss issues and to ensure that only suitable individuals receive the substance. One such training document is the Pharmaceutical Society of Australia's protocol on 'Provision of orlistat as a Pharmacist Only Medicine'. XXXX also stated that it is important that

medical practitioners check for co-morbidities and this is actually facilitated by the greater interaction between the pharmacist and the consumer.

- With regards to the Appendix H listing of orlistat, XXXX believed that branded advertising of orlistat facilitates dialog between overweight/ obese consumers and pharmacists, a better informed community, improved weight loss outcomes and reduced obesity related disorders with diet and exercise and reduced health care costs.
- XXXX documented the allegations made by XXXX against XXXX TVC and noted that only one of these was upheld XXXX, that relating to promotion to an audience wider than the approved indication. XXXX stated that XXXX clearly understand and support the approved indication for orlistat and wished to explain, and apologise for, the error that resulted in the breach.
- XXXX stated that it was XXXX understanding that once orlistat was included in Appendix H, all regulatory requirements to begin advertising XXXX had been met. However, following review of the final TVC script by ASMI, XXXX was made aware of the concept of Restricted Representation as defined in Appendix 6 of the Therapeutic Goods Advertising Code (TGAC). During review of the TVC, the ASMI Advertising Officer noticed the presence of the word 'obesity' on the XXXX pack shot and noted that this must be removed from the pack since obesity is considered a restricted representation. Once this was done, the TVC was approved for airing and XXXX assumed that the TVC had complied with all regulatory requirements. XXXX categorically stated it was never the intention that removal of the word 'obesity' from the pack shot would be interpreted as an attempt to broaden the indication.
- XXXX ceased advertising XXXX following the complaints mentioned above XXXX
- XXXX stated that the partnership between advertising and the pharmacist is critical as the former raises interest, awareness and possibilities for weight loss in the public, whilst the latter operate as the gatekeepers to ensure that only suitable patients receive orlistat.
- XXXX had conducted consumer research which showed that during the short period of advertising orlistat a positive impact was made on public health, with a large number of those surveyed stating that the TVC had motivated them to do something about their weight. XXXX did not provide the data from this research in XXXX submission.
- XXXX believed that removal of branded advertising is likely to see patients denied the opportunity to hear about a highly evaluated, clinically proven medication with an excellent safety record and may well result in patients resorting to the multitude of unscheduled, unproven weight loss products.

A number of submissions were received supporting the continued Schedule 3 and Appendix H listing of orlistat on the basis of public health need. XXXX These submissions all noted that obesity is a growing problem in society and its cost to public health is increasing and that clear benefits have been demonstrated through even a

moderate weight reduction. It was noted that orlistat would achieve this in conjunction with diet and lifestyle modifications. These submissions stated that returning orlistat to Schedule 4 would only serve to limit public access to the substance through reluctance to visit doctors regarding the matter, whether through cost or embarrassment. XXXX stated that restricting advertising of or rescheduling orlistat would be working in opposition to the Governments' National Obesity Taskforce. XXXX noted that orlistat continues to fulfil the criteria for inclusion in Schedule 3 and Appendix H and no information had come to light on the basis of public health and safety which would justify its rescheduling. XXXX stated that to make a non-evidence based decision on these issues would be contrary to the principals of Good Regulatory Practice.

Many submissions supported the Schedule 3 listing of orlistat. XXXX All noted that pharmacists have been provided with appropriate tools and training, developed in concert with the various pharmacy bodies, in order to ensure that orlistat is appropriate for any given patient and that the patient is aware that diet and lifestyle modifications will also need to be made. Pharmacists then use these tools and training to question patients closely to assess whether they are suitable for orlistat use. It is noted that these protocols are enshrined in the legislation of the various pharmaceutical State/ Territory regulatory bodies and they contain very specific advice on the things a pharmacist must consider before they can supply this substance. XXXX stated that these guidelines ensure that orlistat is supplied appropriately and XXXX had not seen evidence to the contrary. XXXX noted that XXXX have been involved in developing these educational materials. Pharmacists are readily accessible to their patients and able to provide ongoing management, care and support with regard to weight loss issues. XXXX noted XXXX have had experience with assisting over 250,000 customers enrolled in weight loss programs. XXXX also stated that pharmacists further contribute to weight management by providing information on healthy lifestyles and developing management plans, identifying target patient groups with a view to providing them with this information and advice on lifestyle change, referring high-risk patients to medical practitioners, assessing the appropriateness of treating patients with orlistat and providing them appropriate medicines and advice on management of these medications. XXXX noted the current indications for prescribing orlistat, that prescribing outside indications is a matter of judgement and that under the SUSDP it would not be illegal for a pharmacist to supply orlistat outside these indications. The Committee noted that supplying a therapeutic good for a use outside of its registered indications is a breach of the *Therapeutic Goods Act 1989*. However they also noted that a pharmacist would need to be able to justify these actions. Indeed they maintained that while requests for supply may have been made by young girls, this had not actually resulted in supply being obtained.

A number of submissions pointed out that orlistat is the only proven safe and effective weight loss substance available to consumers as an over the counter item. These submissions noted that orlistat has a generally good side effect profile and should be used as an adjunct to lifestyle modification. XXXX noted that the safety profile of orlistat has

not changed since 2003 when it was first considered by the Committee, i.e., the safety of orlistat is still appropriate for a Schedule 3 substance.

A number of submissions supporting the retention of orlistat in Appendix H XXXX stated that direct to consumer advertising allows the consumer to be more proactive in their health care and encourages them to seek out solutions regarding health issues from pharmacists. The submissions stated that this may be especially true of patient groups who would not normally see a doctor about such issues. This leads to considerable potential public health benefits, especially with regards to national health priorities such as diabetes and cardiovascular disease, through creating greater consumer awareness of weight loss options. XXXX noted that XXXX had applied for a restricted representation when advertising orlistat which would ensure that any advertising clearly defined the population who qualify to use the substance. XXXX stated that to remove orlistat from Appendix H on the basis of no new clinical evidence would set a difficult precedent for future considerations of the Committee and provide uncertainty to industry when planning for future innovation. XXXX also stated that the TGAC Complaints Resolution Panel is the appropriate regulatory body for issues relating to advertising of this substance. XXXX noted that the advertisement which has been criticised by XXXX had the approval of the relevant regulatory body before it was put to air. XXXX believed that advertising of weight loss substances should only occur when supported by clinical data and should only target adults with established weight problems. XXXX stated that orlistat is the only weight loss substance currently being advertised that has evidence of safety and efficacy and that removing Appendix H listing for this substance would drive consumers back to non-efficacious alternatives. Several submissions made the point that there was a wide body of scientific evidence which supports the safety and efficacy of orlistat, thus Appendix H listing is appropriate provided the substance is marketed in accordance with the Therapeutic Goods Advertising Code.

XXXX provided a submission in which XXXX stated that orlistat is not a drug suitable for inclusion in Appendix H. XXXX also noted that the merchandising for orlistat in October and November 2006 appeared to contravene the requirements of the Victorian Drugs, Poisons and Controlled Substances Regulations 2006 for Schedule 3 poisons; however the sponsor agreed to change this after a meeting with XXXX. Submissions were also received from XXXX supporting this statement.

Various submissions opposed the Appendix H listing and direct to consumer (DTC) advertising of orlistat. These stated that the DTC advertising has lead to inappropriate customers (eg customers whose BMI did not meet the criteria) seeking out the substance and orlistat being provided to them without the involvement of a pharmacist or any significant counselling being provided. XXXX stated that this DTC advertising had, at times, created unreasonable consumer expectation about the substance and that DTC advertising lead them to make their own assessment about their need and suitability for the substance, which may not be correct. This can then cause confrontation and distress between the patient and the pharmacist. XXXX also noted that consumers require more

appropriate forms of medicine information and the context and criteria for use of such than DTC advertising provides.

XXXX provided a submission in which XXXX called for orlistat to be withdrawn as a Schedule 3 substance. XXXX main points were:

- XXXX did not accept the argument that the Appendix H listing of orlistat 'was based on potential public health benefits through allowing consumers to make an informed choice in relation to weight control' and that 'there was an increasing trend for increasing numbers of medicines to be down scheduled.' XXXX stated that orlistat has a significant long term risk of increasing age-related macular degeneration and that this, and the side effect of faecal incontinence, are not mentioned in the advertising. XXXX also stated that XXXX is now known and freely available to consumers suffering from eating disorders, obesity etc in the absence of medical advice and without any education relating to lifestyle changes/ body image.
- XXXX strongly believed that this substance should be a Schedule 4 item as GPs are able to provide the correct counselling about the appropriateness of this substance to their patients who need to lose weight and will prescribe it safely and liaise with the pharmacist when required.
- XXXX stated that the NDPSC's decision to include the substance in Appendix H sets a dangerous precedent. XXXX noted that while consumers want and need information about medications, such a need should not be met by advertising messages which are designed to promote drug therapy above lifestyle changes.
- The danger with advertising came to light recently with the advertising of orlistat during the *Australian Idol* program. XXXX stated that XXXX cannot see any health benefit in promoting a product associated with body image during a program built around, and watched by 'kids' concerned with body image.
- XXXX believed that this substance should be available only as a Schedule 4 item and that the NDPSC should reverse the down-scheduling decision.
- XXXX stated that XXXX have continually raised concern about the NDPSC's decision making process over the last three years. XXXX believed that the orlistat decision reinforces the belief that a lack of practicing medical practitioners on the Committee is a contributory factor in the increasing down-scheduling of substances with serious adverse effects. XXXX noted that the structure of the NDPSC will change with the establishment of the Trans-Tasman Therapeutic Products agency but also stated that the delay in the agency establishment has lead to a postponement of this change and, as such, that the NDPSC continues to make decisions that XXXX have no faith in and that it is essential that this not be allowed to continue.

XXXX, provided a submission in which XXXX supported the continued Schedule 3 availability and Appendix H listing for orlistat. XXXX main points were:

- The implication that pharmacists are unreliable, unethical and unable to provide the required assessment and education to patients is a major concern. XXXX has worked closely with pharmacists in this area and found they are careful in their consideration of orlistat for patients.
- XXXX stated that pharmacists as a profession are concerned about the health of their customers and are willing to undertake more education in order to better serve them. XXXX noted that XXXX had been involved in the education of pharmacists through the PGA and Australian College of Pharmacy.
- XXXX in XXXX professional career had witnessed GPs encouraging patients to speak to their pharmacists about suitable weight loss medications and felt that GPs recognise and support the additional training and experience pharmacists have had in this area.
- XXXX stated that pharmacists occupy a unique position in the community in that they see a much broader population of patients than and are more accessible than other healthcare professionals.
- XXXX stated that XXXX was not concerned about the television advertising of orlistat, rather XXXX felt that it is another means to encourage people to seek advice regarding proven weight loss strategies. XXXX noted that XXXX would have concerns about the advertising of unproven medications available without consulting a pharmacist.

XXXX put forward a proposal to strengthen the SUSDP regulations regarding the advertising of Schedule 3 substances. XXXX suggested that advertising of S3 substances should:

- adhere to the Therapeutic Goods Advertising Code;
- only include registered indications for Schedule 3 status;
- include prominently within the ad that consultation with a pharmacist is necessary;
- reference any restrictions to Schedule 3 inclusion within the ad;
- have a set period to be defined (suggest at least 6 months) implemented between market availability as an S3 product and commencement of advertising rights;
- advertise in media with demographics in line with Schedule 3 restrictions.
- XXXX suggested that in considering this option of modifying the advertising section of the SUSDP, the NDPSC should note the following potential benefits: more national uniformity in regulation; facilitates the granting of Appendix H status by providing a strong national reference code; provides additional support to the Complains Resolution Panel; provides professional guidance to manufacturers; provides professional support to health professionals to ensure responsible advertising of Schedule 3 products.

- Therefore XXXX suggested the following amendment to Part 3 of the SUSDP:

  Paragraph 32. as written

  Paragraph 33. as written

  Paragraph 34. A person advertising a poison listed in Schedule 3 Appendix H must:

  (a) adhere to the Therapeutic Goods Advertising Code,

  (b) include within the advertisement the indication(s) to which Schedule 3 status has been approved, as detailed in Appendix H,

  (c) include the following statement within the advertisement in a prominent manner, i.e. standing out so as to be easily read from a normal viewing distance, and or heard and understood:

  CONSULTATION WITH A PHARMACIST WILL BE NECESSARY TO ADVISE YOU WHETHER THIS PREPARATION [PRODUCT NAME] IS SUITABLE FOR YOUR CONDITION.

  (d) reference within the advertisement of any restrictions to Schedule 3 status, e.g. "regular use for longer than 6 months requires medical attention" or contraindications as detailed in Appendix H, and

  (e) not commence "direct-to-consumer advertising until (set period to be defined – suggest at least 6 months) after actual market availability of the Schedule 3 product i.e., advertising is not permitted for (set period to be defined).

- XXXX also suggested that it may be appropriate in certain instances to include in either Part 4 of the SUSDP or within Appendix H any restricting indications or contraindications.

A Member stated that they had concerns regarding XXXX comment that prescribing orlistat outside its registered indications was a matter of judgement for the pharmacist. The Member stated that, while this was strictly correct, the down scheduling of orlistat occurred on the basis that orlistat was to be used for the approved indications only. The Member also felt that there were ethical concerns relating to the actions of a pharmacist in this scenario, as similarly there would be concern relating to a doctor prescribing and holding an interest in a pharmacy. The Member felt that in this instance that a pharmacist must apply a high ethical standard as the profit motive may be seen to conflict with professional standards.

XXXX provided a submission in which they supported the continued inclusion of orlistat in Schedule 3 of the SUSDP but opposed the Appendix H listing of the substance. XXXX believed that pharmacists have the correct tools and knowledge to assess patient appropriateness for orlistat but that direct to consumer advertising can lead to patients having false expectations about their suitability for this substance. To enable the

pharmacist to help explain orlistat requirements to the consumer XXXX believed that consumers would require more appropriate forms of medicine information and the context and criteria to explain the schedule. Brand advertising did not create the right environment or context to deliver these types of information to consumers.

XXXX provided a submission in which XXXX supported the continued Schedule 3 availability and Appendix H listing of orlistat. XXXX main points were:

- In their letter to the NDPSC (available on Choice's website), Choice detailed three main concerns: (1) 'we have heard anecdotal evidence from pharmacists that girls as young as 13 with a BMI of less than 25 have already been asking for the drug.' (2) that the product was inappropriately advertised (3) that *'..Roche has set a precedent and that other pharmaceutical companies will apply to change the schedule of their drugs, in order that they may advertise direct to consumers and thus find a loophole through the regulations on direct-to-consumer advertising.'*
- XXXX put forward the following arguments regarding Choices' 3 concerns:

  (1) The availability of any product will lead to inappropriate requests (eg laxatives) whether the product is available on prescription, Schedule 3, Schedule 2 or general sale. What matters is whether these requests are dealt with correctly according to relevant protocols.

  (2) The CRP has made a ruling on Choice's complaints regarding the advertisements and save for the issue of the advertisements not including more information regarding indications for use, these complaints had been dismissed.

  (3) The comments made by Choice were nonsensical given it is the role of the NDPSC to consider scheduling changes and the appropriate level of advertising that may accompany any change.
- XXXX has been associated with the development of pharmacy and pharmacist protocols for the appropriate dispensing and sale of orlistat as an S4 substance since 2001 and as a Schedule 3 substance since it was rescheduled in 2003. These materials emphasise the need for both non-pharmacological intervention and support, as well as that non-pharmacological measures are preferable as first-line treatment.
- XXXX also produced a substantial amount of material that was mailed to all its members at the time. Training sessions for pharmacy staff were held by both organisations around Australia and, in the case of XXXX, these had continued throughout 2006 and will reoccur in 2007 as they seek to ensure that pharmacists and pharmacy assistants have the knowledge, skills and tools to ensure that protocols are followed.
- XXXX stated that it seems clear that XXXX is of the view that, once advertised, orlistat can be purchased at a pharmacy by a consumer with little, if any, intervention by staff. This was not correct and flies in the face of established professional protocols and training given to pharmacy staff as detailed above.

- Patients often request a product/medicine that is inappropriate for their circumstances and it is in these cases that a health professional acts as a 'learned intermediary'. Given concerns regarding obesity and its social impact, XXXX was of the view that it is preferable to use advertising that complies with the Code to inform the public of treatment options and for subsequent requests by consumers to then be a matter for decision by the appropriate health care professional, and where any treatment or advice can be given in the context of on-going support. In the absence of such information and support, consumers would source whatever is available, often without access to any intervention by a healthcare professional.
- Returning orlistat to Schedule 4 and/ or refusing Appendix H status would therefore effectively send a message that medical practitioners were the only health professionals qualified to make such decisions and, by implication, they always make correct decisions. There is no evidence to support this implication, whereas documentation suggests that, for pharmacists, pharmacy professional organisations had gone to some lengths to train and prepare them in the use of this substance.
- As the current consideration was prompted by XXXX campaign, including anecdotal reports of requests for inappropriate supply, and not by any new evidence on the safety or efficacy of the substance, it would be inappropriate to overturn the original, evidence based decision of the Committee.

On February 7, 2007 the Food and Drug Administration (FDA) in the United States of America approved 60mg orlistat (in Australia the dose is 120mg) as an over-the-counter weight loss aid for overweight adults over 18 years of age when used in conjunction with a reduced-calorie, low-fat diet and exercise regime. XXXX had also notified the Committee of this decision.

A Member noted that the Committee had no role in the application of sanctions for breaches related to the advertising of substances included in Appendix H. Members agreed that this was the role of the CRP.

A Member felt that the submissions from XXXX were significant and highlighted the concerns regarding the direct to consumer advertising leading to inappropriate requests for the substance and potential confrontation between the pharmacist and the patient and that this type of advertising can overwhelm the public health message for the substance.

The Committee agreed that XXXX might have more appropriately directed XXXX concerns regarding the results of the Shadow Shop and pharmacist practice to the Pharmacy Board of NSW as this is the appropriate body for dealing with practice mismanagement. It was suggested that the Committee should write to the Pharmacy Boards voicing its concerns. A Member questioned the validity of the 30 pharmacies that were chosen for the shadow shop exercise, stating that they were concerned that the pharmacies may have been chosen because XXXX had information that the pharmacies may be undertaking questionable practice with regard to this substance. The Committee

agreed however, whether the pharmacies were targeted or not, that the results were concerning.

A Member stated that the XXXX shadow shopper did give quite significant evidence of inappropriate availability of orlistat. The Member noted that there were deficiencies in the type of survey used but that the result was not unambiguous. The Member questioned if it had been mentioned in the survey if whether advice had been given about the need for vitamin supplementation as this is something that is stated in the PI and may be related to adverse events. Another Member noted that nothing specific had been mentioned and that the survey stated that only 16 of the 24 pharmacies who sold the substance to the shopper mentioned the side effects of the substance.

The point was made that the Committee needed to be clear that there were two decisions that needed to be made: one regarding scheduling and the other regarding Appendix H listing. A member stated that the Committee had not been given much additional information that would give rise to a reconsideration of scheduling. The Member further noted that XXXX also conduct a regular mystery shop survey of XXXX pharmacies as part of XXXX program and the Committee should be loathe to take a very small selection of pharmacies as from XXXX and draw conclusions from this. The Member stated that the item came to the Committee as a consequence of advertising issues and advertising and scheduling issues often get caught up particularly in peoples minds.

A Member noted that the Committee had to recognise the existing advertising controls and that the system does work as it identified the breach and placed sanctions on the sponsor company. The Member noted that XXXX had made some recommendations regarding the strengthening of advertising controls within the SUSDP, but the Member felt that these recommendations should be referred to the Advertising Code Council as they were the appropriate body for any such comments.

A Member stated that the FDA decision could be seen as an endorsement of the Committee's previous decision. A Member stated that despite the differences (60mg in the USA compared to 120mg in Australia) between the FDA and NDPSC decision, the FDA's decision to make orlistat available OTC validates the decision the NDPSC made to down-schedule orlistat from Schedule 4 to Schedule 3. Another Member felt that, as the FDA decision was quite different to the Australian scheduling of orlistat, it was not particularly relevant to the Committees' considerations.

A Member stated that there were 2 main issues in pharmacy practice around this substance. First, that there are many weight loss products on the market for which there is no evidence for and it is difficult to get patients to realise that orlistat does work. Second is that if patients come in and say that they want product x XXXX then it is difficult to get a clinical conversation started as with the direct to consumer advertising of these substances they have predetermined ideas for what will suit them. Another Member questioned why this was not the case with orlistat. The Member stated that such a clinical

conversation is easier with orlistat as there are guidelines that the pharmacist can refer the patient to when they are discussing the issue with the patient.

A Member reiterated that the Committee had not been presented with any new evidence that patients are not able to diagnose themselves with obesity and that there was also no evidence associated with harm from use of the product arising from any misdiagnosis. The member stated that there were a lot of misguided statements in the submissions received about the long-term safety of the substance and that the Committee had looked at this data before and had put it aside as there had been no particular concerns raised about the safety. The Member also noted that the Committee did not know whether pharmacists were following the protocols. The Member stated that both Australia and New Zealand do have an obesity epidemic and that given the seriousness of this, multiple public health interventions are needed at multiple levels to intervene in trying to turn that around and that doctors and pharmacy both have a role in this, as do patient groups and the education of patients through as many routes as possible. The Member stated that advertising was a double-edged sword but it was one of the ways that public awareness of the issue is raised and awareness of a treatment that is proven to work. The Member also stated that while the advertising system failed in the approval of the advertisement, that the complaints system did resolve the issue by identifying the issue and taking corrective action. The Member noted that in this resolution it was shown that a number of the assumptions made by XXXX about the viewing population of *Australian Idol* were incorrect.

A Member pointed out that the advertising of unscheduled substances is not the purview of the NDPSC and therefore irrelevant to these discussions. The Member reminded the Committee of the current approved indications for orlistat and the Member noted that the indications clearly referred to a number of co-morbidities. The Member then referred to the NDPSC criteria for including a substance in Schedule 3 which clearly state that Schedule 3 medicines are for ailments or symptoms which can be identified by the consumer and verified by the pharmacist and do not require medical diagnosis or only require initial medical diagnosis and do not require close medical management. The Member also noted that under the indications for use section the guidelines stated that the ailment or symptoms being treated should not require close medical management or direct supervision by a doctor and be easily recognised with assistance from a pharmacist and that they be amenable to short-term treatment or monitoring by the consumer with assistance from a pharmacist. The Member then stated that all of these criteria apply to a patient that is mildly overweight, but not to a patient who has a BMI of 27 with the co-morbidities mentioned, as all of these require close medical management. The Member further stated that it is the responsibility of the Committee to determine whether orlistat meets the requirements of Schedule 3 status according to the guidelines and the registered indications of the product.

The Committee agreed that the decision to down-schedule orlistat was properly considered against the NDPSC guidelines over a number of meetings. The Committee

also recalled that the decision to down-schedule was primarily based on public health issues as increasing access to orlistat would benefit public health. Another Member raised the point that the guidelines state that Schedule 3 substances should be used for conditions which don't require medical diagnosis and the co-morbidities do require such diagnosis and on-going medical care. A Member noted that the presence of co-morbidities is only required if the patients BMI is between 27 and 30, if the patient has a BMI over 30 then they are not required to have these other factors. A Member stated that the patient may be under medical care and that the medical practitioner may have views about whether orlistat is appropriate for that patient and the Committee should be taking that into consideration. Another Member stated that their recollection of the discussion was based on public health issues and that if you increased access to the substance that you would be benefiting overall public health.

A Member stated that the criteria for Schedule 3 substances were developed on balance and the Committee had included orlistat in Schedule 3 after a great deal of consideration and intense discussion of the criteria due to concerns about getting the balance between the criteria and the risk/ benefit balance for the patient right. The Member also stated that they did not believe that the pharmacy environment was fundamentally flawed on the basis of XXXX survey. The Member felt that the issues relating to the pharmacist performance should be referred to the relevant boards but that the results did not necessarily show that orlistat is inappropriately scheduled.

A Member noted that there had been new data submitted to the Committee showing that the advertising as a consequence of Appendix H listing has put extra stress on pharmacists through patients arriving with the expectation of being given the substance and that this data should be considered with regard to the Appendix H listing and Schedule 3 inclusion of the substance. The Member stated that such patient expectations were making it difficult for pharmacists to then refuse supply and that this undermined placing the substance in Schedule 3.

A Member recalled that the Committee took the view that the safety profile of orlistat was appropriate for Schedule 3 listing and that the greater good would be served by encouraging people to use it if the pharmacists were taking responsibility for dispensing it, giving the patients the right advice and monitoring its use. The Member also recalled that the Committee believed that the advertising of orlistat would be in the public interest.

The Committee was reminded that this substance is only indicated for a small subset of the obese population. The Member also noted that this subset of patients require medical management for their condition. Another Member recalled that the data the Committee looked at showed that orlistat does not interact with anti-hypertensives, anti-diabetics, in fact the Committee noted a study which showed that orlistat had positive effects on diabetic control and cardiovascular risk factors as well as weight. The Member stated that that there were no immediate safety or interaction issues and that the Committee took the view that a patient with a co-morbidity would be under medical care for that condition.

Whilst this is the case, concern was still raised that advertising orlistat direct to consumers may not be appropriate given the very small group it is approved for use for.

Members noted the specific patient population that orlistat would currently be appropriately advertised to (i.e., patients with a BMI of 30, or 27 with other risk factors).

A Member noted that the data provided by the sponsor showed that the sponsor advertised to all different age groups and that the *Australian Idol* audience is made up of a number of different demographics and on balance the CRP felt that there was not unfair targeting of a young audience and the sponsor have stated that that was not their intention. The Member also noted that advertising had been booked across a wide range of programs and that the Committee needed to accept that assessment from the CRP. The Member stated that the issue was that the advertisement did not reflect the indications for use of the substance, and thus there was a perception that they were extending the use of the product to the broader population who are overweight. The Member stated that the Committee does not have a role in promoting good public health, weight loss, exercise and diet, rather it is the Committee's purview to consider the scheduling of orlistat against the criteria set in its own guidelines.

A Member stated that there had not been any new risk/ benefit data for orlistat presented to the Committee which would predicate a reconsideration of the scheduling of the substance. Another Member stated that the Committee did not necessarily have to be presented with evidence of a safety problem to review the decision and that the Committee should look at the initial decision and the guidelines again with fresh eyes.

A Member stated that it must be considered that pharmacists do not work isolation but that they work in conjunction with other healthcare professionals and the Members should remember that the pharmacist also has the opportunity to direct the patient to different avenues for weight loss such as dieticians or other healthcare professionals. The Member stated that the Committee needed to be cautious on its emphasis of the substances' indication, as while, in terms of making sure that the indication is being seen correctly, orlistat is not being positioned as a magic bullet and, in fact, forms a very small part of the arsenal. It was argued that the Committees guidelines regarding what is appropriate for a Schedule 3 substance are very specific and that orlistat patients generally have co-morbidities which require medical management. It was pointed out that the indication for orlistat was for weight management, not for the management of any associated co-morbidities and that a pharmacist is not required to manage and diagnose these co-morbidities. The pharmacist should question the patient as to whether they have the associated risk factors and whether they've seen their doctor about them, then they can work out whether orlistat is the right medication for the patient.

A Member raised the point that there is a move towards self-management of longer term conditions and in the UK that there are a number of substances which are available as a pharmacist only substance and these conditions are being managed long-term in pharmacy.

However, Members noted that the points regarding the indications of orlistat had been well made and the Appendix H decision should be revisited since orlistat is only indicated for a very small subset of the overweight population and any advertising should target the actual indications.

It was suggested a watching brief on the use and misuse of orlistat as a Schedule 3 substance is made by the Secretariat and that the Committee should also inform other expert Committees, such as ADRAC, that the NDPSC is interested in any safety concerns with the substance should they come to light.

DECISION 2007/49 - 17

While acknowledging the importance of the obesity problem in Australia, the Committee decided that, on balance, there was insufficient public health benefit associated with allowing direct-to-consumer advertising of orlistat. Orlistat is currently only indicated for use in a relatively small group of patients with serious and significant weight problems (those with a Body Mass Index (BMI) greater than 27 with other serious diseases, or those with a BMI greater than 30), not for the general population who might wish to manage more minor weight issues. The Committee noted the advice from professionals and consumers that direct-to-consumer advertising increased pressure on pharmacists to provide orlistat to consumers. This in turn had the potential to result in inappropriate patterns of use, in patients for whom orlistat was neither indicated nor appropriate. By retaining it in Schedule 3, the Committee has ensured that orlistat remains available for appropriate patients with professional advice from pharmacists.

Appendix H – Amendment

Orlistat – Delete entry.

11.4 TOPICAL CORTICOSTEROIDS –ALCLOMETASONE, CLOBETASONE, MOMETASONE

PURPOSE

The Committee considered the current scheduling of the topical corticosteroids alclometasone, clobetasone and mometasone.

BACKGROUND

Alclometasone

Alclometasone dipropionate is a semi-synthetic chlorinated corticosteroid used topically for its glucocorticoid activity in the treatment of various skin disorders. Glucocorticoids have multiple mechanisms of action including potent anti-inflammatory activity,

immunosuppressive properties, and antiproliferative actions. Anti-inflammatory effects result from decreased formation, release and activity of the mediators of inflammation which reduce the initial manifestations of the inflammatory process. The immunosuppressive properties decrease the response to delayed and immediate hypersensitivity reactions. The antiproliferative effects reduce hyperplastic tissue characteristic of psoriasis.

Alclometasone was first considered by the Committee at the May 1988 Meeting and was included in Schedule 4 following advice from the ADEC that it had recommended marketing approval for XXXX cream and ointment.

The February 2000 NDPSC Meeting agreed on the rescheduling of alclometasone in preparations for dermal use containing 0.05 per cent or less of alclometasone in packs containing 30 g or less of such preparations from S4 to S3. The decision was made on grounds of comparable potency, efficacy and safety of alclometasone 0.05% with 1% hydrocortisone, an S3 drug. The NDPSC subsequently forwarded a recommendation to the New Zealand MCC to consider adopting a similar outcome. However, MCC rejected this proposal on the advice of XXXX that the S4 classification remained appropriate. The May 2001 NDPSC Meeting reconsidered its decision at the request of the New Zealand MCC, and agreed to seek expert advice.

At the November 2001 NDPSC Meeting, the Committee received advice from XXXX which raised concern over the absence of reliable safety data on the long-term use of topical alclometasone. The NDPSC noted submissions which recommended the retention of the S3 classification from XXXX highlighting the importance of labelling and pharmacist counselling. The NDPSC also noted from XXXX that there had been 4 adverse reports associated with topical alclometasone XXXX between 1988-1996, all of which were minor and application site reactions occurring after short periods of use (less than a week).

The NDPSC agreed not to harmonise the scheduling of alclometasone with New Zealand at the February 2002 meeting on the basis that there was sufficient evidence to demonstrate that the safety profile and pattern of use of such preparations justified their continued availability as an S3 medicine.

At the February 2005 meeting, the Committee agreed to recommend to the New Zealand Ministry of Health that alclometasone be rescheduled to restricted medicine (Schedule 3), on the basis of established safety in use and to achieve harmonisation.

At the October 2006 NDPSC Meeting, the Committee considered an application to include alclometasone 0.05% in preparations for dermal use in Appendix H of the SUSDP. The Committee discussed the information presented by the sponsor as well as pre-meeting submissions. The Committee also considered information relating to the potency and adverse event profile of this corticosteroid and other moderately potent agents, as the side-effect profiles of alclometasone and mometasone (48/10.1) were both

compared to hydrocortisone 1% and clobetasone 0.05%. Given the concerns about potential adverse events with these agents, Members agreed that the safety and AE profile of moderate to potent topical corticosteroids (alclometasone, mometasone and clobetasone) should be reviewed as a whole. Thus, the Committee agreed to defer all scheduling and Appendix H decisions for moderately potent topical corticosteroids pending the foreshadowed consideration of all moderately potent corticosteroids at the February 2007 Meeting, when further data is received from XXXX, given the concerns regarding potential adverse events experienced with moderately potent corticosteroids.

Mometasone

Mometasone furoate is a corticosteroid used topically for its glucocorticoid activity in the treatment of various skin disorders. It is usually employed as a cream, ointment, or lotion containing 0.1% mometasone. When applied topically (particularly to large areas, when the skin is broken, or under occlusive dressings), or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Mometasone undergoes extensive first-pass hepatic metabolism.

The August 1992 Australian Drug Evaluation Committee Meeting recommended approval of mometasone furoate for treatment of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses, including psoriasis and atopic dermatitis. Approval was also recommended for treatment of psoriasis of the scalp and seborrhoeic dermatitis. The February 1993 DPSCC Meeting subsequently agreed to include a Schedule 4 entry for mometasone furoate. The August 1999 NDPSC Meeting amended this entry to the parent compound mometasone following a TTHWP recommendation.

The November 1999 NDPSC Meeting agreed to reschedule mometasone to Schedule 3 for use in aqueous nasal sprays for the treatment of season allergic rhinitis (with certain dose and age conditions). The May 2000 NDPSC Meeting subsequently agreed to include mometasone in Appendix H. The October 2002 NDPSC Meeting agreed to extend the indications for mometasone in Schedule 3 to include "for the short term prophylaxis or treatment of perennial allergic rhinitis". The June 2003 NDPSC Meeting agreed to reschedule mometasone for the short term prophylaxis or treatment of allergic rhinitis, with dose and age restrictions, to Schedule 2 (and as there was no longer a Schedule 3 entry, mometasone was deleted from Appendix H). Mometasone in aqueous nasal spray for use outside the Schedule 2 restrictions (as well as all other mometasone preparations) remained Schedule 4. Minor editorial amendments to this entry were subsequently agreed to at the February 2004 and October 2005 NDPSC Meetings.

The June 2006 NDPSC Meeting agreed to reschedule 0.1% dermal mometasone preparations from Schedule 4 to Schedule 3 on the basis that the evidence provided by the sponsor adequately met the criteria for Schedule 3 inclusion, and that the concern in relation to inappropriate use of this potent corticosteroid would be waylaid through appropriate pharmacist eduction prior to product launch. The Appendix H inclusion was

not supported by the Committee at this stage due to a lack of OTC experience for this potent corticosteroid.

At the October 2006 NDPSC meeting, the Committee considered XXXX post meeting comments XXXX received regarding the June 2006 decision (2006/47-22) to reschedule topical mometasone to S3. The Committee also considered a letter from XXXX which was received after post meeting comments closed, however the Committee felt it was relevant to the Committees' consideration of the issue. After discussion of these submissions and discussion of concerns regarding the adverse event profile of mometasone, the Committee decided to set aside the June 2006 decision (2006/47-22) and foreshadow consideration of the scheduling of mometasone, alclometasone and clobetasone at the February 2007 meeting pending receipt of further information regarding the adverse event profile of these substances.

Clobetasone

Clobetasone butyrate is a corticosteroid used topically for its glucocorticoid activity in the treatment of various skin disorders. It is usually employed as a cream or ointment containing 0.05%. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. The effects of topical corticosteroids on the skin are described on. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see. Clobetasone butyrate is also used for inflammatory eye disorders, as eye drops containing 0.1%. Prolonged application to the eye of preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Clobetasone was first included in S4 of the SUSDP at the March 1980 DSPCC Meeting, with no cut-offs to less restrictive Schedules.

In forwarding a pre- November 2001 Meeting submission relating to alclometasone, XXXX included a proposal that the NDPSC consider rescheduling from S4 to S3, dermal preparations containing 0.05% or less of clobetasone in packs containing 30 g or less. XXXX had argued that clobetasone was in the same class as alclometasone, being a moderately potent corticosteroid. Furthermore, XXXX forwarded an additional proposal prior to the February 2002 meeting, seeking to include clobetasone in Appendix H of the SUSDP – Schedule 3 poisons permitted to be advertised.

XXXX had planned to market a product in Australia, XXXX, containing 0.05% clobetasone butyrate in a pack size of 30 g. The proposed indication was for short-term treatment (7 days) and control of patches of eczema and dermatitis, including atopic and seborrhoeic eczema, and primary irritant and allergic dermatitis on certain areas of the body for use in adults and children over 12 years of age. Following the November 2001 meeting, XXXX was advised that the Committee had deferred consideration of its

proposal relating to clobetasone to the February 2002 meeting, to allow a proper evaluation of its submission.

No product containing clobetasone was listed on the ARTG or PUBCRIS. The Medsafe database listed dermal preparations (cream and ointment) containing 0.05% clobetasone in 30 g and 100 g tubes.

The NDPSC noted comments from XXXX and also XXXX which supported the proposal that dermal preparations containing 0.05% or less of clobetasone in packs containing 30 g or less, be rescheduled to S3.

The NDPSC recalled that it did not adopt the New Zealand MCC recommendation to reinstate in S4, preparations containing 0.05% alclometasone for dermal use. Members were reminded that the NDPSC proceeded to confirm the S3 scheduling of 0.05% alclometasone for dermal use, on the basis that there was sufficient evidence to demonstrate that the safety profile and pattern of use of such preparations justified their continued availability as S3.

The NDPSC was advised that the relative potencies of clobetasone and alclometasone were comparable, and that the safety profile and efficacy of 0.05% alclometasone is similar to 1% hydrocortisone. Accordingly, alclometasone was also approved for use in children under 2 years old. It was noted that whilst clobetasone has comparable side effect profile to 1% hydrocortisone cream, XXXX submission was based on the proposed use of 0.05% clobetasone in adults and children 12 years and over.

At the February 2005 NDPSC Meeting, the Committee reviewed the Schedule 3 (S3) entries for clobetasone and alclometasone in relation to whether these entries should be limited to single active ingredients only. The Committee expressed a concern over the absence of safety data of combination products and considered it appropriate for future applicants to provide adequate evidence of safety and efficacy to allow such combination products to be considered for inclusion in Schedule 3. Therefore, the Committee agreed to amend the Schedule 3 entries for clobetasone and alclometasone to limit them to single active ingredient formulations only, taking into account their existing safety profile.

The S3 dermal corticosteroids, 1% hydrocortisone and 0.05% clobetasone are currently included in Appendix H.

DISCUSSION

The Committee recalled the following from the October 2006 NDPSC Meeting:

- XXXX submitted an application seeking approval to include alclometasone 0.05% XXXX in Appendix H to allow branded advertising to consumers.

- The Committee considered post-meeting comments from XXXX in relation to its June 2006 decision to reschedule 0.1% dermal mometasone preparations from Schedule 4 to Schedule 3.
- Members agreed that there was currently no post-market experience with alclometasone dipropionate 0.05% for topical use in either the Australian or New Zealand market. Members recalled that the Committee had previously decided to reject the inclusion of mometasone furoate 0.1% in Appendix H due to a lack of OTC market experience.
- Members recalled that at the June 2006 NDPSC Meeting, the Committee agreed to down-schedule mometasone, a potent corticosteroid, from Schedule 4 to Schedule 3. However, after post meeting submissions were received, as well as correspondence from XXXX all highlighting the incidence of AEs with mometasone, the Committee had agreed to set aside the decision to reschedule mometasone (2006/47-22) pending further advice from XXXX. While there was no comparison in potency between alclometasone and mometasone in the application, XXXX submission to reschedule mometasone made a point that mometasone possessed "…the equivalent side-effect profile to hydrocortisone 1% and clobetasone 0.05%". As the side-effect profile of mometasone and alclometasone were both compared to hydrocortisone 1% and clobetasone 0.05%, Members agreed that the safety and AE profile of moderately potent topical corticosteroids (alclometasone and clobetasone) should also be reviewed as a whole and further data be sought from XXXX.

XXXX provided a pre-Meeting submission in which they reasserted their view that the correct decision was made at the June 2006 Meeting. XXXX main points were:

- Mometasone furoate 0.1% topical preparations have been available for many years on prescription and the request to reschedule topical mometasone is for short term use of a related set of skin disorders in adults and children over the age of 2 years. The current Schedule 2 intranasal preparations are indicated for short term use only.
- Other corticosteroid preparations (alclometasone, clobetasone and hydrocortisone) have already been reclassified based on their risk/benefit. While mometasone is a more potent corticosteroid, risk/benefit reviews suggest that non-halogenated ester-type topical corticosteroids such as mometasone furoate are in fact less likely to cause contact allergy and adverse effects than the halogenated corticosteroids. The Committee noted that mometasone furoate is indeed a halogenated corticosteroid
- Adverse effects observed in patients in clinical trials were usually transient, mild or mild to moderate with an incidence that was either similar to or less than that observed with the comparator glucocorticoid. The most frequently observed ADRs were stinging, burning, pruritus, folliculitis, dryness, tenderness and (rarely) signs of skin atrophy. This ADR pattern is also reflected in the reports to ADRAC where application site and skin reactions were the most common. A recently requested ADR report shows a total of 152 reports to ADRAC since 1994 for mometasone furoate and of these 19 are for rosacea or telangiectasia and while many do not indicate the

onset time of the reaction, those that do suggest it is far in excess of the 28 days proposed for OTC use.

- Low and medium potency steroid creams and ointments have been available as OTC medicines for more than 10 years in Australia and overseas without clinically significant adverse effects. Several clinical trials comparing mometasone furoate 0.1% with other topical steroids have confirmed that short-term use of mometasone resulted in no clinically significant difference between hydrocortisone 1%, clobetasone 0.5% and betamethasone 0.1% in terms of skin thinning or other side effects which were normally mild and transient. A tabulated summary comparing clinical trials and ADRs between momestasone, hydrocortisone, betamethasone and clobetasone was provided.
- Reports of cutaneous atrophy occurring after treatment periods of more than 3 weeks have been reported in the literature with several of the topical corticosteroids, however the studies with mometasone furoate 0.1% in adults and children have shown that when used once a day for up to 4 weeks, minimal side effects occur. In four of the published safety and efficacy studies, steroid induced rosacea (telangiectasia) is mentioned as a possible side effect, however many of the reports relate to usage far in excess that proposed by the OTC regimen and the majority of other studies did not report telangiectasia, including studies where application regimes were more intensive than the proposed OTC preparation.
- XXXX acknowledged that a major risk with the topical use of potent glucocorticoid preparations is their potential to cause hypothalamic-pituitary-adrenal (HPA) axis suppression. However in several randomised, double-blind, parallel group, or non-blind studies in healthy male volunteers and patients with allergic rhinitis or psoriasis, administration of mometasone either by nasal, oral or topical routes did not produce any clinically significant decrease in serum cortisol levels, and no symptoms of HPA axis suppression were observed. The proposed indications for mometasone furoate are for once a day application for up to four weeks treatment. Studies have shown that even when three times more than the normal application is used for more than three weeks, side effects are mild and transient. XXXX believed that the pack size (30g), labelling and pharmacy intervention with each sale will provide adequate safeguards to ensure proper short term use of this substance.
- XXXX
- XXXX quote a post-meeting response XXXX which suggested that a Schedule 3 indication for mometasone should exclude psoriasis and chronic conditions; limit the age range to 12 years and above and limit the pack size to 15g. However, considerable evidence has been derived from nearly 20 years experience which shows that the current use in adults and children aged 2 years and above is adequate with no unexpected safety concerns. Further, other OTC preparations do not have the same restrictions so to include them for mometasone, which has a demonstrated safety profile, is inappropriate. With regard to pack size, the amount of product required depends on the extent of the dermatoses. In one particular trial XXXX of

mometasone was used at each application, which is a much greater use of product than would be expected and this use was only associated with very mild side effects over a 21 day period. It was clear then that while a 30g pack size may provide a sufficient amount for limited dermatoses it would not be sufficient to induce any side effects. To limit the pack to 15g would only cause the patient unnecessary expense and inconvenience by having to purchase multiple tubes within the 4 week period. Multiple purchases of the product could well encourage complacency on the part of the patient and thus may have the opposite to the intended effect.

- XXXX quote another post-meeting responder XXXX who also objected to the rescheduling, based on safety and potential for adverse events. By the nature of the comments, it would seem that these may have been provided by either a member, or section, of the medical profession, however no scientific evidence appeared to have been included, only anecdotal reports of side effects. The original application made by XXXX provided peer review clinical safety and efficacy studies to support the rescheduling of mometasone which have been properly evaluated (the evaluator concluded: "mometasone furoate has no major effects on skin atrophy. Although mometasone was found to be clinically and statistically superior to hydrocortisone in psoriasis, there was a low potential for overt skin atrophy, only occurring in a few patients over 6 weeks. Thus, it would be reasonable to expect that the once-daily application for up to 4 weeks with OTC use is not likely to present any significant problems"). In the absence of any further scientific evidence which would refute many years of use and published papers XXXX believed the original decision should stand and mometasone furoate should be rescheduled to Schedule 3.

XXXX provided a pre-Meeting submission in which XXXX gave information regarding XXXX noted a number of concerns regarding the rescheduling of mometasone and XXXX did not support inclusion of mometasone in topical preparations in Schedule 3 of the SUSDP. XXXX main points were:

- XXXX noted the NDPSC October 2006 Record of Reasons and the concerns raised regarding pharmacist education requirements, and the potential for an increase in adverse events with OTC use of mometasone. XXXX also noted that claims that similar corticosteroids have been reclassified to non-prescription status were disputed, as mometasone is significantly more potent than topical corticosteroids currently in Schedules 2 or 3, such as hydrocortisone and hydrocortisone acetate, clobetasone or alclometasone.
- XXXX noted that objections to the rescheduling of this substance had been received by professional organisations and that if it was rescheduled that it would be the first halogenated corticosteroid available as an OTC substance. XXXX also noted that mometasone is stronger than, and has a different adverse reaction profile to, any of the currently available OTC topical corticosteroids.
- XXXX queried whether, given the NDPSC concerns, inclusion of topical mometasone products in Schedule 3 is appropriate under any conditions and XXXX

noted that if topical mometasone is included in Schedule 3, there would likely be further applications to the NDPSC for inclusion of other halogenated corticosteroids in Schedule 3**.**

- XXXX contended that there is no pressing need for such a potent substance to be available to the public without prescription, that currently available OTC corticosteroids should suffice in most OTC circumstances, prolonged use of topical corticosteroids may cause HPA axis disturbance and that prolonged use of topical corticosteroids on the face may cause rosacea and prolonged use may also cause skin atrophy.
- XXXX concluded that NDPSC should be advised that XXXX does not support the inclusion of topical mometasone in Schedule 3. However, XXXX recommended that if the NDPSC does reaffirm its June 2006 decision, the maximum pack size of OTC products should be restricted to 15 g XXXX.

XXXX provided a submission in which XXXX provided information regarding adverse events with topical mometasone and opposed any change in scheduling. XXXX also provided email confirmation that XXXX have no concerns regarding the scheduling of alclometasone and clobetasone. XXXX main points were:

- Topical corticosteroids are not a new form of treatment and indeed are the mainstay of topical dermatological therapy. However, when these very useful agents are used inappropriately, significant adverse effects may occur. The majority of these adverse effects will be seen cutaneously and systemic adverse effects are unlikely to occur if mometasone were to be listed as a Schedule 3 item as very limited quantities would be available. However, if it was a child being treated and the parent or guardian were to go to a number of different pharmacies, it would be possible for the child to be exposed to sufficient corticosteroid to cause a systemic reaction.
- An article entitled “Adverse effects of topical glucocorticosteroids” was published in the *Journal of the American Academy of Dermatology* in January 2006 and the authors of the article stated that “despite encouragement to report adverse drug reactions, the clinical practice of reporting is poor and incomplete”, a statement XXXX agreed with. XXXX stated that it was likely that every XXXX had seen the adverse effects of mometasone overuse including rosacea, perioral dermatitis, acne, as well as the extra facial adverse effects of striae, atrophy and purpura but that XXXX do not report them as they are so common. XXXX also stated that this paucity of reporting likely gives inappropriate reassurance that these medications are without adverse effects.
- Different sites absorb topical corticosteroids to different extents. Whilst it maybe appropriate for an individual to apply mometasone ointment to a lichenified, infiltrated area on the forearm where absorption may be as low as 1%, the patient may be under the misapprehension that being a pharmacist-only agent, that it would be safe and could be used on other sites. If such an agent was to be applied to areas such

as the face where increased amounts of corticosteroids are absorbed, local side effects will be more common and more pronounced.

- The following adverse events are caused by over/ inappropriate use of mometasone:

  Atrophy- Intertriginous areas such as the axilla, groin folds and submammary area are particularly susceptible, due to increased temperature, moisture, the occlusive effect of skin on skin and the thinner skin present. Atrophy is the most common adverse effect of topical corticosteroid therapy.

  Telangiectasia – occurs, particularly on areas such as the face, due to corticosteroids stimulating dermal microvascular endothelial cells. As a consequence, capillaries and arteries abnormally dilate causing prominent vessels.

  Striae - caused by cutaneous atrophy with the deposition of collagen along the lines of mechanical stress.

  Steroid rosacea and perioral dermatitis - characterised by papules and pustules which clear with the use of topical corticosteroids but recur with increased severity upon cessation, on a background of erythema, are commonly seen on in patients who have been using mometasone on their face.

  Hypertrichosis - characterised by the growth of vellus hairs.

- Whilst the appropriate use of topical corticosteroids to treat inflammatory dermatoses in the majority of cases does not cause significant adverse effects, their use may cause problems and this is much more likely to occur if patients are mistakenly using the therapy on inappropriate sites on the understanding that there is no limits as to how often, how widely or where the therapy is applied as it is a non-prescription item.
- According to the seven class ranking of topical corticosteroid preparations, mometasone ointment is ranked as Class 2 (potent) and is therefore considered stronger than other prescription items such as triamcinolone acetonide, betamethasone valerate and methylprednisolone. Given this and the adverse event profile of the substance, XXXX does not support the rescheduling of this agent.

XXXX provided a submission regarding the rescheduling of clobetasone in which it supports a continued Schedule 3 listing for this substance. XXXX main points were:

- Clobetasone has been available in Australia as a Schedule 3 medicine for some years as well as the UK for approximately 5 years and more recently, in New Zealand. Clobetasone has a long history of safe use (over 20 years) with a low incidence of adverse events.
- Pharmacists are able to guide patients in recognising the symptoms of common skin diseases, making self-diagnosis and treatment by consumers appropriate. Pharmacists are also able to provide information to the consumer which would assist them in using the product appropriately.

- Keeping this moderately potent corticosteroid as an OTC medication would provide a significant public health benefit.
- The substance has a low potential for abuse or for masking a serious underlying condition.
- There is a low incidence of systemic and topical toxicity, with data showing that short-term use of clobetasone by adults and children is not likely to cause significant degrees of skin atrophy or HPA axis suppression.
- Both the MCC (11/ 2000 and 7/ 2005) and NDPSC (2/ 2002) had previously considered the scheduling of clobetasone and there has been no change to the safety profile of the substance since this time. At these considerations the conclusion was drawn that clobetasone has the evidence to support its safe use in the OTC environment if appropriate labelling is implemented and training given to pharmacists on its use.
- Regarding the MCC's concerns that pharmacists may not be able to diagnose or may misdiagnose eczema and dermatitis and that patients may apply cream to their faces, XXXX had worked extensively with XXXX in New Zealand on these issues. XXXX had been working in conjunction with XXXX to develop an appropriate training program to aid pharmacists in the differential diagnosis of eczema and dermatitis as well where fungal infections are implicated. The issue of application of the substance to the face is addressed by appropriate pack labelling and the package insert for the product.
- XXXX had also worked with XXXX to develop appropriate training for Australian pharmacists.
- Given the above, XXXX felt that clobetasone still meets the criteria for a Schedule 3 substance.

XXXX provided a submission in which XXXX provided comment on the scheduling considerations for mometasone and alclometasone. XXXX main points were:

- Mometasone – XXXX did not support the proposal to reschedule topical mometasone furoate 0.1% from Schedule 4 to Schedule 3 or the inclusion of the substance in Appendix H of the SUSDP.
- XXXX reiterated the points made in XXXX May and August 2006 submissions to the NDPSC regarding the proposed rescheduling of this substance.
- Further to this, XXXX noted that diagnosing skin conditions is difficult. XXXX cited a recent study *(Tran H, Chen K, Lim AC, Jabbour J, Shumack S. Assessing diagnostic skill in dermatology: a comparison between general practitioners and dermatologists. Australas J Dermatol. (2005) Nov;46(4):230-4)* showing that only 58% of GPs provided a provisional diagnosis in their referring letter and among all referrals, only 42% had a diagnosis that corresponded with that determined by dermatologists. The authors concluded by stating that there was a need to improve GPs' diagnostic skills

through education. Given this, XXXX stated that for patients, recognition of a condition would most likely be based on recurrence of a previous medically-diagnosed condition.

- XXXX stated that the treatment of psoriasis with topical corticosteroids requires close supervision, particularly when treating chronic, thickened or hyperkeratotic dermatoses, which require treatment with potent or very potent agents. XXXX noted that the British Association of Dermatology guidelines state that 'potent corticosteroids should not be used for more than seven days' and that 'use of potent or very potent preparations should be under dermatological supervision'.
- The treatment of dermatitis would be the main condition where patients would benefit from increased access to more potent topical corticosteroids. However, XXXX felt that there was no clinical need for increased access to mometasone and this was supported by a recent review which found that acute dermatitis flare-ups are well treated with mild or moderate topical corticosteroids. Further, the British Association of Dermatology guidelines for the management of atopic eczema state that 'regular review of steroid use in terms of potency and quantity (especially when using potent steroids) is essential' and that 'patients using moderate and potent steroids must be kept under review for both local and systemic side-effects'. Such a review may not be possible in most pharmacies within the current Australian pharmacy setting.
- XXXX noted the UK example where clobetasone butyrate 0.05% is the most (moderately) potent corticosteroid available as an OTC agent for the treatment of dermatitis and stated that this is suitable as a higher strength corticosteroid which is available to consumers to treat dermatitis flare-ups.
- XXXX also stated that down scheduling of mometasone could lead to a situation where it is used preferentially to treat skin conditions which could just as easily be treated by a mild or moderate potency substance. XXXX noted that there are a number of mild or moderate corticosteroids currently available as OTC substances, however there are other moderately potent agents which are still contained in Schedule 4 for dermal use.
- XXXX noted a comment from the Record of Reasons from the June 2006 NDPSC Meeting which stated that if a real need exists for down scheduling a higher potency corticosteroid, then consideration should be given to down-scheduling other moderately potent (Class II) corticosteroids that are currently on the market.
- XXXX noted that, given the medical need of the conditions being treated and the current availability of suitable products, there is no need for a more potent agent to be available as a Schedule 3 substance.
- XXXX also discussed the risk of harm from inappropriate use or abuse of the substance. XXXX noted that at the June 2006 NDPSC meeting, the Committee considered that the adverse event profile of mometasone was comparable to that of hydrocortisone 1% and clobetasone 0.05%. However, the data considered by the Committee was generated from the 15g pack size, not the proposed 30g cut-off limit

that is proposed for the Schedule 3 entry, i.e., the data for the 15g pack is being used to support a Schedule 3 entry for a pack twice its size. It should also be noted that this data was generated under the current scheduling arrangements where medical supervision is required for the use of this substance.

- Regarding the under-reporting of adverse events for mometasone that was noted at the October 2006 NDPSC Meeting, XXXX referred to comments made by the MCC in November 2002 where Members agreed that 'adverse effects relating to these concerns [skin thinning, use on the face and long-term use] were probably not widely reported. Not a great deal of research had been conducted in this area and available data were patchy.'
- XXXX agreed that harm from inappropriate use of this substance is a major concern and refers to data from the December 2005 edition of the Prescriber Update published by the Pharmacovigilance Centre, New Zealand which noted a number of reports of facial skin damage including telangiectasia, rosacea and skin atrophy.
- XXXX also referred to a 1993 study by *Kesckes et al* which looked at the use of mometasone outside its registered indications compared to another potent corticosteroid. The study found a significantly higher incidence of adverse events with mometasone compared to the other agent. XXXX noted that this is especially relevant to the community setting as patients can easily apply the product inappropriately.
- XXXX noted that the NDPSC Guidelines for inclusion of a substance in Schedule 3 of the SUSDP state that said substance should show a low potential of abuse and harm from inappropriate use.
- XXXX further noted that the NDPSC Guidelines for inclusion of a substance in Schedule 3 of the SUSDP state that said substance should show a low incidence of side effects which are likely to require medical intervention.
- XXXX stated that the risk-benefit profile of mometasone is favourable when the product is used appropriately under close medical supervision and notes that the PSUR (July 2001 – May 2006) for XXXX shows that is the case with a total of 417 ADRs being reported for the period, 21 of which were ‘serious’ as defined by the PSUR criteria. The majority of events reported were application site reactions. This data shows that there is a substantial incidence of ADRs which could potentially require medical intervention or assessment, notwithstanding the fact that currently the product is only used under medical supervision.
- Therefore, given the potential for inappropriate use, harm from such use, the need for medical intervention in adverse events and the possible underreporting of adverse events, it is not appropriate to down schedule this substance to Schedule 3 and include it in Appendix H. XXXX also noted that inclusion of this substance in Schedule 3 without indications or age restriction would compromise the safe use of the product.

- Alclometasone - XXXX noted the favourable evaluation report from the NDPSC evaluator and concurred with the view expressed by a Committee member at the October 2006 NDPSC Meeting that inclusion of alclometasone in Appendix H would not lead to increased consumer access to this substance.
- XXXX also stated that the consideration of this matter should be independent of the Committees' consideration of the rescheduling of mometasone, particularly since the two have a different potency classification: alclometasone dipropionate is moderate (Class II), whilst mometasone is classified as potent (Class III).

A Member pointed out that the data provided by XXXX regarding mometasone AEs was still anecdotal and, thus, at the lower end of the scale of the hierarchy of evidence. The Member also noted that there were reasonable clinical trial and post-marketing data that suggest that mometasone probably does have a comparable side effect profile to hydrocortisone 1%, so that the increased potency does not seem to translate into greater adverse events in the formal clinical studies setting. The Member stated that the question in their mind was whether mometasone is used to treat the more severe end of the spectrum of conditions or if there are greater issues with safety, whether there's inappropriate use of mometasone in such patients, however there are no direct data that are available on that point. The Member also noted that the potency of topical corticosteroids is based on a bioassay and wondered whether the potency is expressed on a molar basis, i.e., that the concentration of 0.1% mometasone being used is $1/10^{th}$ of the hydrocortisone 1% and thus, even though the substance is biologically more potent, the adverse events do not translate into clinical practice as less of the substance is being used.

The Committee was, on the whole, disappointed with the calibre of the submission received from XXXX. It was noted that a quick search of PubMed revealed a number of relevant articles on the relative safety profile of topical mometasone, while XXXX claimed that AEs are widely underreported and this infers that no clinical data on relative safety profiles is available.

A Member noted that none of the pre-meeting submissions revealed major concerns raised regarding whether alclometasone and clobetasone should remain in Schedule 3 and the Member felt that they should remain there. The Member also stated that with regard to the Appendix H listing of alclometasone and clobetasone, there have been no Schedule 3 preparations of either substance available in Australia, therefore there is no experience with the use of these substances in the over-the-counter environment. The Member felt that this experience would need to be gained before Appendix H listing was appropriate for either substance.

The Committee was reminded that the Schedule 3 inclusion of clobetasone and alclometasone was done as part of the Trans-Tasman harmonisation process and that there did not seem to be any issues raised regarding the current scheduling of these substances.

The Committee agreed that, while the data provided to the Committee by XXXX was only anecdotal, the Committee had also been provided with a lot of clinical and comparative data with regards to the adverse event profile of mometasone.

The Committee was informed that the MCC was concerned that it was likely that if a more potent corticosteroid (such as mometasone) entered the market then it would be used preferentially as a first line treatment to other, less potent agents as the perception would be that the more potent steroid would have to be better. Therefore, the MCC felt that it was important that there be created an opportunity for pharmacists to be educated about, and have a treatment ladder for the use of these agents. This way it would ensure that the patient would start off treatment with the less potent agents and then only move up to the medium potency agents if the initial treatment failed and that if these agents failed then the pharmacists would refer the patient to a medical practitioner.

Another Member noted that the alclometasone and clobetasone products are not currently marketed in New Zealand or Australia as over-the-counter (OTC) agents, therefore there is no experience in Australasia with the use of moderate potency topical corticosteroids as OTC agents. The member stated that it would therefore make a lot of sense to gain experience with the moderate potency agents OTC before making higher potency agents available OTC. The member also noted that internationally that there is no Western country that has a high potency topical corticosteroid available as an OTC agent but that there is some experience with moderate potency topical corticosteroids XXXX OTC in the UK. The Member also felt that higher potency may also mean more masking of conditions potentially and also that if a substance is available OTC people do consider it to be safe and this may lead to more AEs from inappropriate use, particularly on the face. The Member felt that it should be seen first whether this occurs with the medium potency steroids before allowing high potency steroids in Schedule 3.

On the issue of relative potencies, a Member reiterated that there had been valid concerns shown by the Committee that the usual practice for scheduling was to gain experience with agents in particular schedules before allowing more potent agents to be down scheduled and as there was no experience with medium potency topical corticosteroids in an OTC environment it would not be unreasonable to gain that experience before moving to down schedule more potent agents.

Members discussed whether alclometasone and clobetasone should retain their current Schedule 3 status. A Member noted that there was some precedent in the harmonisation process around scheduled products which had not been marketed being moved back to Schedule 4. Another Member noted that both these substances were Schedule 3 in New Zealand, due to Trans-Tasman harmonisation. The Member noted that no additional data had been provided for these two substances and that communication had been received from XXXX which stated that XXXX had no concerns with the current scheduling of these two substances.

Members discussed the Appendix H listing of both clobetasone and alclometasone. A Member noted that the substances can be readily advertised in New Zealand. The Member also noted that hydrocortisone is included in Appendix H.

A Member stated that there was some sense in the treatment ladder approach for the advertising of these substances as well. The Member noted that there has been long experience with hydrocortisone, that it is advertised direct to consumers so patients know about it and if it doesn't work there is available in Schedule 3 two more potent agents for pharmacists to recommend to patients if appropriate. The Member was concerned that allowing advertising of clobetasone and alclometasone would cause a shift in patient usage patterns to requesting these more potent agents as a first line therapy. The Member stated that the agents would be advertised as more potent and, given there is no experience with them as OTC agents, that Appendix H listing is not appropriate at this time for these agents.

A number of Members noted that branded advertising would lead to the patient asking for the product by name which thus may potentially remove the clinical conversation from the pharmacist. The Members felt that, until there was experience with that clinical discussion, the substances should not be included in Appendix H.

OUTCOME

The Committee agreed that, due to the need to first gain experience with lower potency corticosteroids as Schedule 3 substances, that the current scheduling of mometasone remains appropriate at this time.

Further, the Committee agreed that, given there were no emerging safety concerns regarding the Schedule 3 listing of clobetasone and alclometasone, the current scheduling of clobetasone and alclometasone remained appropriate at this time.

DECISION 2007/49 - 18

The Committee agreed, due to their similar safety profile and the need to gain experience with the Schedule 3 use of the substances before allowing the advertising of them, to remove clobetasone from Appendix H of the SUSDP and not to include alclometasone in Appendix H of the SUSDP.

Appendix H – Amendment

Clobetasone – Delete entry

11.5 PARACETAMOL 665 MG TABLETS

PURPOSE

The Committee considered an MCC recommendation to harmonise on the requirement for S2/pharmacy-only tablets or capsules containing over 500mg and up to 665 mg of paracetamol to be in slow release form only.

BACKGROUND

The October 2001 meeting of the TTHWP had agreed to a process leading to harmonisation of entries for paracetamol in 2004 based on foreshadowing scheduling changes arising from the handover by the NDPSC of Appendix F warning statements for therapeutic goods to the TGA.

In the December 2001, the MCC considered the classification of paracetamol 665mg. MCC had agreed to differ on the upper limit for OTC sale and had retained the 500mg per dose form upper limit. They had also agreed to increase pack sizes to 12.5 grams to harmonise with Australia.

New Zealand had advised that it was to review regulatory standards and labelling standards for paracetamol before further addressing the harmonisation of scheduling. In that regard, XXXX advised that revised regulatory guidelines for paracetamol would be developed for the Joint Agency. The "*Required Advisory Statements for Medicine Labels*" was issued in July 2004. On this basis, the TTHWP recommended that the scheduling of paracetamol 665mg be referred to MCC for consideration.

The MCC reconsidered the classification of paracetamol 665mg in their June 2006 Meeting, and agreed to harmonise with Australia for this product.

At the October 2006 NDPSC meeting the Committee considered a recommendation arising from the June 2006 MCC meeting that the NDPSC be asked to harmonise with New Zealand with regards to the requirement for S2/pharmacy-only tablets or capsules containing over 500mg and up to 665 mg of paracetamol to be in slow release form only. After discussion of the request and the reasons behind it, the Committee agreed to foreshadow consideration of the scheduling of paracetamol at the February 2007 meeting.

DISCUSSION

The MCC considered the classification of paracetamol 665 mg tablets at their June 2006 meeting. The Committee recalled the following points:

- The MCC had earlier been concerned that possible confusion of 665mg slow release products with lower dose 500 mg products could result in overdosing. However,

members acknowledged that the 665 mg tablets had been available in Australia for approximately four years and over-dosing did not appear to be a problem.

- An ongoing concern was that emergency rooms might not be aware of slow release paracetamol products and therefore of the need to retest overdose patients with equivocal levels of blood paracetamol. Members agreed that they would like assurance from the company that a protocol for appropriate treatment would be provided for emergency rooms.

- Most members agreed that there was benefit to consumers in having a slow release product three times daily to provide pain relief throughout the night rather than the usual four doses for 500 mg tablets.

- The MCC agreed to harmonise with Australia on the classification of 665mg paracetamol tablets and that the NDPSC should be asked to harmonise on the requirement for S2/pharmacy-only medicines over 500 mg and up to 665 mg per tablet or capsule to be in slow release form only.

XXXX all provided submissions agreeing with the proposed rescheduling of paracetamol 665mg. XXXX noted that the likelihood of a tablet containing more than 500mg paracetamol being produced was small and that such a product would be required to be evaluated for registration by the TGA.

XXXX provided a submission which agreed that the appropriate scheduling for slow-release forms of paracetamol is Schedule 2 or above. However, XXXX stated that tablets or capsules containing over 500 mg and less than 665 mg paracetamol should not be restricted, if these are immediate release preparation with a dose not greater than 1000 mg. XXXX main points were:

- TTHWP acknowledged that overdose with immediate release 665mg tablets did not appear to be a problem and that the main concern surrounding overdose was with sustained release formulations due to the fact that emergency rooms may need to repeat testing of paracetamol blood levels.
- This is an opportunity to examine the current wording of the paracetamol schedule entries, in order to simplify and reduce the complexity of the current wording while maintaining appropriate restrictions.
- To simplify the scheduling of paracetamol, the SUSDP entries should be worded such that they reflect that individual dosage units should not exceed 1000 mg (regardless of the dosage form) and that the recommended maximum dose taken at each interval should not exceed 1000 mg paracetamol. The exception to this would be in the instance of slow release paracetamol, which while individual dosage units are less than 1000 mg (i.e. *650* mg), the required individual dose is two tablets (is 1300 mg).
- XXXX suggested the following wording be adopted for the paracetamol entries:

Schedule 2
PARACETAMOL for therapeutic use **except**:

(a) when included in S4

(b) in immediate release, divided preparations, each containing 1000 mg or less of paracetamol as the only therapeutically active constituent other than an effervescent agent when:

(i) the labelled recommended individual dose not exceeding 1000 mg paracetamol;

(ii) enclosed in a primary pack that contains not more than 12.5g paracetamol;

(iii) compliant with the requirements of the ***Required Advisory Statements for Medicine Labels;*** and

(iv) not labelled for the treatment of children *6* years of age

(v) in the instance of tablets or capsules, packed in blister or strip packaging or in a container with a child-resistant closure.

Schedule 4
PARACETAMOL:

(a) when combined with aspirin, caffeine or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;

(b) in slow release tablets or capsules containing more than *665* mg paracetamol

(c) in other divided, immediate release dosage units containing more than 1000 mg paracetamol.

- The proposed amended entry would have no regulatory impact as it retains maximum pack contents of paracetamol available GSL and limits GSL preparations to immediate release forms only.

A member noted that the main concern of the MCC was to keep the idea that paracetamol was at 500 mg except in special dose forms and if the upper limit for all dose forms was moved to 665 mg it could mean that doses with unusual amounts of paracetamol could occur in the marketplace. The member stated that the MCC felt that keeping the 500 mg limit for all dose forms kept a level of control over the dose available to the public.

Members discussed the proposal put forward by XXXX and noted that it would allow immediate release formulations of up to 1000 mg being available as unscheduled medicines. Members agreed that patients generally believe that paracetamol is very safe and that you take two tablets of paracetamol per dose. Members further agreed that this could lead to problems with overdose and toxicity with the higher dose immediate release paracetamol formulations.

DECISION 2007/49 – 19

The Committee agreed, given the safety concerns surrounding the potential for overdose and toxicity with immediate release doses of paracetamol over 500 mg and in order to harmonise the scheduling of paracetamol with New Zealand, to amend the Schedule 4 entry for paracetamol.

Schedule 4 – Amendment

PARACETAMOL – Amend entry to read:

PARACETAMOL:

(a) when combined with aspirin, caffeine or salicylamide or any derivative of these substances except when separately specified in these Schedules;

(b) in slow release tablets or capsules containing more than 665 mg of paracetamol;

(c) in non-slow release tablets or capsules containing more than 500 mg of paracetamol; or

(d) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol.

11.6 TRANEXAMIC ACID

PURPOSE

The Committee considered harmonising the scheduling of tranexamic acid with New Zealand.

BACKGROUND

The February 2000 NDPSC meeting supported an application that tranexamic acid for the treatment of menorrhagia be rescheduled to Schedule 3 and that it also be included in Appendix H. This decision was made on the basis that:

- Schedule 3 would allow appropriate monitoring of safety in OTC use;
- that menorrhagia was a condition appropriate for OTC treatment under professional supervision;
- advertising would increase consumer awareness that this was a treatable condition; and
- there was a public health benefit associated with Schedule 3 availability and advertising.

In making this decision, the Committee noted that treatment for menorrhagia could not be advertised under the current TGA Code, but that the sponsor would seek exemption from this restriction if the Committee approved inclusion in Appendix H.

The Committee also agreed that tranexamic acid be included in Appendix F with Warning Statement 54: Seek medical advice before the first course of treatment.

Tranexamic acid was raised during harmonisation consideration at the June 2006 TTHWP and NDPSC meetings. However, at the NDPSC meeting, the New Zealand MedSafe Member advised the meeting that the June 2006 MCC meeting did not support harmonisation with Australia. The NDPSC agreed to defer further consideration of tranexamic acid pending receipt of the June 2006 MCC minutes.

At the October 2006 NDPSC meeting, the Committee considered the minutes of the June 2006 MCC meeting which stated that the MCC did not change the scheduling of tranexamic acid to a pharmacist only medication and that the NDPSC be asked to consider harmonising the scheduling for this substance. The Committee was advised by the New Zealand MedSafe Member for the reasons behind this decision and discussed this rational with regards to the Australian scheduling of the substance. After due consideration of these issues, the Committee agreed to foreshadow consideration of the scheduling of tranexamic acid for the February 2007 Meeting.

DISCUSSION

The Committee recalled the following points from the October 2006 NDPSC meeting:

- The June 2006 MCC meeting did not agree to harmonise with Australia based on safety concerns surrounding self-diagnosis:
  - diagnostic testing (normally by ultrasound) was necessary to determine the cause of menorrhagia, which is not possible for an OTC medicine;
  - potential masking of more serious conditions;
  - inability to accurately diagnose underlying cause of menorrhagia within the pharmacy.

- During their consideration, MCC noted that XXXX had not provided a response during the consultation period and that no OTC product for this indication had been marketed in Australia.
- MCC requested that NDPSC reconsider its S3 scheduling of tranexamic acid to harmonise with New Zealand.
- Only two tranexamic acid products are registered in Australia, XXXX
  - XXXX
- XXXX did not provide any comment concerning harmonisation with New Zealand.

DECISION 2007/49 - 20

The Committee agreed to harmonise the scheduling of tranexamic acid with New Zealand by deleting the Schedule 3 tranexamic acid entry and amending the Schedule 4 entry.

Schedule 3 - Amendment

TRANEXAMIC ACID – delete entry.

Schedule 4 – Amendment

TRANEXAMIC ACID – Amend entry to read:

TRANEXAMIC ACID.

Appendix H – Amendment

Tranexamic acid – delete entry.

11.7 SUMATRIPTAN

PURPOSE

The Committee further considered a proposal to include oral preparations containing 50 mg or less of sumatriptan in packs containing 2 dosage units or less for the treatment of migraine attacks in Schedule 3 (S3) and Appendix H of the SUSDP.

BACKGROUND

Sumatriptan is a selective serotonin agonist that acts at 5-hydroxytryptamine$_{1B/1D}$ receptor subtype (5-HT$_{1B/1D}$) receptors. Activation of 5-HT$_{1B}$ receptors produces vasoconstriction of cranial arteries while activation of 5-HT$_{1D}$ receptors on nociceptive trigeminal nerve afferents reduces the release of vasoactive neuropeptides and inhibits transmission via

second-order neurons of the trigeminocervical complex. These actions correlate with relief of migraine headache.

Sumatriptan was first considered by the Committee at the August 1992 meeting where it was included in S4 of the SUSDP. It was next considered at the June 2005 NDPSC Meeting, where the Committee considered a proposal to include 2 tablets x 50mg or less of sumatriptan in Schedule 3. The Committee felt firstly that there was no suitable, validated diagnostic tool available to pharmacists to accurately diagnose migraine and further that there were concerns about the safety of the substance, particularly its cardiovascular and cerebrovascular side effects and the high prevalence of these in the community. Given this, the Committee agreed that sumatriptan should remain a Schedule 4 substance.

At the June 2006 NDPSC Meeting, the Committee considered a new proposal to include oral preparations of sumatriptan 50mg in packs of 2 tablets for the treatment of migraine attacks in S3 and Appendix H. The Committee was informed XXXX had provided an updated dossier for consideration, which has taken into account the June 2005 NDPSC Record of Reasons. Concerns were raised over the possibility of patients overusing sumatriptan and the emerging evidence that sumatriptan may not be entirely 'migraine specific'. Therefore, the Committee decided to seek advice from XXXX on these issues and to defer a decision on the rescheduling of sumatriptan until such advice was provided.

At the October 2006 NDPSC Meeting, the Committee further considered the rescheduling proposal which had been deferred from the June 2006 Meeting. The Committee discussed the advice received from XXXX and further information provided by the sponsor in relation to the concerns raised at the previous meeting. The Committee also discussed emerging evidence of a possible interaction between sumatriptan and serotonergic antidepressants causing serotonin syndrome. Due to these concerns relating to the potential for concomitant use of triptans and serotonergic antidepressants to precipitate serotonin syndrome, the Committee agreed to again defer a decision on the rescheduling and Appendix H listing of sumatriptan pending review of emerging safety data obtained from the Adverse Drug Reactions Advisory Committee (ADRAC) regarding this interaction.

DISCUSSION

XXXX provided a XXXX post-meeting comment addressing the arguments, in particular the possibility of serotonin syndrome, raised in the Record of Reasons of the October 2006 Meeting. Members noted the following:

- In response to the issue of ADRAC serotonin syndrome reports and the ADRAC Bulletin article in February 2004, XXXX noted that of the 161 cases of serotonin syndrome reported to ADRAC, not one had been associated with the use of a triptan, however XXXX also noted that there is potential for this syndrome to occur when a

patient taking a serotonergic agent is prescribed another one. XXXX also stated that pharmacists are already aware of this potential and that the issue is not restricted to possible interaction with prescription drugs, as St John's wort has been associated with the syndrome.

- XXXX pointed out that the Migraine Questionnaire would prompt customers to tell pharmacists about any other medications they were using and thus, the pharmacist would be aware if the patient was taking any other medications associated with serotonin syndrome. The pharmacist would then be able to counsel the patient in the symptoms of serotonin syndrome.
- XXXX noted that in April 2006 the FDA requested all triptan manufacturers add class labelling for triptans regarding the concomitant use of SSRI/ SNRIs and the potential for serotonin syndrome. XXXX reviewed XXXX and found no causal relationship between sumatriptan use alone or concomitantly with SSRI/ SNRIs. However XXXX updated XXXX to reflect the FDA request. XXXX proposed that the wording in the OTC PI for sumatriptan be amended in line with the prescription PI, apart from the final statement in the Warning and Precautions section which would reflect the OTC use of the product. The new wording (underlined) of the proposed document would be "*There have been rare postmarketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) with sumatriptan .If concomitant use of sumatriptan and an SSRI/ SNRI is to be considered appropriate, migraneurs should be warned to see their doctor if they develop symptoms of serotonin syndrome* XXXX
- XXXX was concerned at the wording used in the Record of Reasons for the October 2006 Meeting in relation to the use of the term "emerging safety concern" to describe the potential interaction of sumatriptan with SSRIs. XXXX contended that the potential for the interaction with SSRIs is not an 'emerging safety concern' as it was currently included in the PI for the prescription product and the proposed PI for the OTC product.
- The migraine questionnaire should only be provided to a customer after the pharmacist has already assessed that OTC analgesics are not providing adequate relief and that the headaches described have some of the characteristics of a migraine headache. XXXX stated that this approach would be covered in the training provided to pharmacists before the launch of the product and that these materials have been reviewed and discussed at 2 expert panels. Membership on these panels included pharmacists with expertise in pharmacy education, neurologists and general practitioners. XXXX also noted that there would be continued development of these materials in collaboration with the abovementioned groups.

XXXX provided a submission in which XXXX stated that XXXX strongly oppose the inclusion of sumatriptan in Schedule 3 and especially Appendix H. XXXX made the following points:

- An advertisement's principal and ultimate purpose is to increase sales and because modern advertising techniques are skilful and pervasive, the goods are effectively "sold" in the living room.
- An accurate diagnosis of migraine is essential and there are fears that advertising may lead consumers to think they have a migraine when their headache is from another cause.
- Currently advertisements for substances in Appendix H do not inform the consumer that the substance is not available on request, rather only after a pharmacist has determined there is a genuine therapeutic need for it. This can cause difficult situations for a pharmacist when they have to explain why they are following legal and professional obligations which detracts from their role in determining whether the medication is required. XXXX felt that sponsors should be obliged to inform the consumer of this requirement, perhaps through wording such as "Your pharmacist is required to determine whether this medicines is suitable for your use" which would then allow the pharmacist to perform their role properly.
- XXXX noted that sumatriptan could have drug interactions with other commonly prescribed agents, such as anti-depressants and that this may lead to serotonin syndrome. They also noted that there was a risk that patients may have undiagnosed subarachnoid haemorrhage instead of a migraine and state that, as diagnosis of this is difficult for a physician, then it would be much more so for the public. Thus, XXXX felt that treatment with sumatriptan should only be under medical direction.
- XXXX concurred with XXXX on the above issues and XXXX also provided a submission supporting XXXX stance on the issue.

XXXX provided a submission regarding adverse events with sumatriptan. This submission did not support the down-scheduling of the substance. XXXX main points were:

- XXXX had noted the July 2006 FDA alert warning of the potential for *'a life-threatening condition called serotonin syndrome [that] may occur when triptans are used together with a SSRI or a SNRI'*. Similar warnings were subsequently published in the October issue of CMAJ (Wooltorton E. Triptan migraine treatments and antidepressants: risk of serotonin syndrome) which noted that the FDA had received 27 reports of serotonin syndrome (SS) in association with triptans plus an SSRI/ SNRI. However, given the large number of reports of this condition with antidepressants alone, this was considered a very small number and suggested a low risk. This information was considered at the November 2006 XXXX.
- Over 9000 adverse event reports had been received by XXXX for SSRIs, of these less than 20 involve concomitant use of a triptan and only 2 of these involved serotonin syndrome, however neither of these were clear cut SSRI- sumatriptan interactions. XXXX

- The experience of both the FDA and the Australian reporting systems appeared to indicate a low risk of serotonin syndrome in association with the use of sumatriptan together with an SSRI or SNRI. However, there is a strong theoretical risk of interaction between these drugs and warnings of possible SS are detailed in the relevant PI documents. Given this, it is possible that appropriate prescribing and avoidance of an interaction has contributed to the apparently low risk of SS with triptans when taken in combination with an SSRI or SNRI.
- SS is a severe and life-threatening disorder and when it does occur it has been precipitated by the first or second dose of a triptan. Therefore lowering the pack size to 2 tablets would not necessarily lower the risk of SS developing with concomitant use of antidepressants.
- XXXX were particularly concerned that there was a high risk that sumatriptan could be recommended for use inappropriately if medical advice and assessment was not provided. In addition to SS, sumatriptan and other triptans are associated with other rare but potentially life threatening adverse events, such as coronary artery vasospasm in those with or without underlying cardiovascular disease. Further, these drugs are indicated for migraine that has been diagnosed by a medical practitioner and are contraindicated in hemiplegic, basilar, and ophthalmoplegic migraine and it is unlikely that the use of sumatriptan in these contexts could be managed without medical intervention and advice.
- Overall, XXXX considered there was a small risk for severe, life threatening reactions with sumatriptan that was unlikely to be mitigated by restricting the pack size to 2 tablets. Sumatriptan-sensitive migraine is not a condition that could be diagnosed without medical assessment and in the absence of medical advice and assessment, there was a relatively high risk that sumatriptan could be dispensed inappropriately, for example to those with known or unknown cardiovascular and other disorders in which the drug is contraindicated.
- XXXX acknowledged that supply of medicines under Schedule 3 of the SUSDP required advice from a pharmacist and XXXX considered it reasonable to expect that pharmacists would be in a position to ask consumers about concomitant medicines, thereby avoiding prescribing sumatriptan in combination with antidepressants or other contraindicated drugs; and to provide patients (*via* a CMI) with information on the safe use of sumatriptan. However, it is a long-standing concern to XXXX that pharmacists are not fulfilling their obligations in relation to providing information about medicines to patients; and there were no adequate mechanisms to compel them to do so. XXXX also considered it unreasonable to expect pharmacists to provide a correct diagnosis of the specific type of migraine sumatriptan is indicated for and advice of situations where sumatriptan should and should not be used.
- XXXX also considered the potential public health benefits of down-scheduling sumatriptan and agreed that the primary benefit related to a change in accessibility for known migraine sufferers, who are generally advised by their doctor to have a supply

of medication on hand. Relaxing access so that undiagnosed migraine suffers could access sumatriptan was not considered a benefit and indeed was considered a risk.

- Given these concerns regarding safety and appropriate use and supply, XXXX did not consider it appropriate that sumatriptan be down-scheduled to Schedule 3. XXXX also believed strongly that sumatriptan should not be used for patients who had not been correctly diagnosed and assessed for contraindications. In this context, sumatriptan would not be suitable for inclusion in Schedule 3 because of the potentially serious consequences of inappropriate supply.

XXXX provided a submission in which XXXX provided further information regarding XXXX rescheduling proposal, particularly with regard to the interaction between sumatriptan and SSRI/ SNRIs and serotonin syndrome. XXXX main points were:

- In April 2006, the FDA requested all US triptan manufacturers to add class labelling for triptans regarding the use of SSRIs/ SNRIs. This action took place after FDA reviewed 27 US reports of serotonin syndrome in association with concomitant triptan and SSRI/ SNRI use XXXX review of this data identified that 19 of these cases involved sumatriptan.
- The 19 cases were reported over a period of more than 12 years since the product was launched in the US and during this period it is estimated that over 40 million migraine attacks have been treated with sumatriptan. Evaluation of the data showed that while the tablet formulation accounts for approximately 80% of all migraine attacks treated with sumatriptan, only 8 of the 19 cases were confirmed as being associated with administration only by the oral route. The number of cases is proportionally far higher for the injection formulation with 7 of the 19 cases associated with administration by this route.
- XXXX had been aware of the theoretical potential for the serotonin syndrome and for many years labelling for sumatriptan as a prescription product has described the possibility of a rare interaction between sumatriptan and SSRIs and the development of weakness, hyperreflexia and incoordination.
- The FDA case report data suggest that while the serotonin syndrome interaction is possible, it actually occurs very rarely, particularly if taken by the oral route. Further, after a review of XXXX found no convincing evidence to support a causal relationship between the use of sumatriptan alone or concomitantly with an SNRI and the development of the serotonin syndrome.
- Despite this XXXX acceded to the FDA request and amended the PI for OTC sumatriptan to include information about a potential reaction with SSRI/ SNRIs and a more accurate description of serotonin syndrome. XXXX

A Member noted that XXXX did not have any reports of serotonin syndrome with sumatriptan and SSRIs, so the concern is based on the FDAs requirement for the changes to be made to the PI documents. The Member stated that with the right intervention at pharmacy level, identifying what other medications that the patient is on, that this is a

manageable situation and perhaps there should be a cut-off point where patients who are on SSRIs/ SNRIs are not able to get the substance at Schedule 3. The Member noted that the patient faces the same risk if they go to a doctor and the doctor prescribes them sumatriptan while they are on an SSRI. The Member stated that they didn't see that a rare potential interaction as being an insurmountable reason for disallowing a substance being available in pharmacy, especially if there was an appropriately structured questionnaire and treatment algorithm available.

Another Member noted that the concerns raised XXXX were not to do with the possibility of serotonin syndrome rather, that Schedule 3 status did not improve accessibility to the substance to diagnosed migraine sufferers who generally have a supply of sumatriptan with them from their doctor and that there was also potential for masking other conditions.

A Member noted that the MCC had considered this and noted that diagnosed migraine patients do not always have a prescription from their doctor and that for these patients that the consideration was whether supply of the substance through pharmacy would significantly increase the persons risk over and above the alternative, such as them phoning their doctor and requesting a script. The MCC considered that there was no increased risk to these patients with the substance being available in pharmacies. The Member noted that in order to ensure this the words 'well characterised' were used in the MCC OTC classification. This would also ensure that if the patient presented with anything else the pharmacist would refer them back to their doctor. A Member questioned whether MCC had sought the advice of Medicines Adverse Reactions Committee (MARC) in relation to this matter. It was confirmed that the MCC had not sought advice from this body. A Member noted that the Committee had not had the benefit of viewing the evidence New Zealand had used to make their rescheduling decision and that the advice that the Committee did have was from an Australian expert advisory Committee and XXXX who had advised that they did not think rescheduling this substance was appropriate. A Member noted that the MCC had looked at the data that was in the MARC database, but that the advice of MARC had not been sought as their focus is not on whether a medicine is safe enough to be reclassified. The Member also noted that the makeup of the MARC Committee was markedly different to that of ADRAC and that it does not have a neurologist on the panel.

A Member noted that other than the safety issue, the other argument for having the substance more widely available is whether it would serve an unmet clinical need if down-scheduled The Member felt that there was not a lot of evidence supporting down-scheduling as most patients get a prescription and tend to then keep several days supply of tablets. The Member stated that they had not seen any data to support the theory that having the substance available as a Schedule 3 substance means that patients obtain the substance more rapidly.

A Member noted that, in relation to the opinion of expert groups, previously the Committee had encouraged such groups to provide data which would help the Committee

in making its decisions but not actually ask the groups for their opinion on the scheduling matter as these groups generally do not have all the criteria, the comparative information or data submissions that the Committee has access to. The Member also stated that the Committee needed to be careful not to ask for such opinions on scheduling as it is the purview of the Committee to make such decisions, but instead to seek their input and ask them to, when possible, provide such input in the context of the criteria set out in S52E of the *Therapeutic Goods Act 1989*.

A Member stated that it seemed as though the submissions from XXXX were more concerned with the potential advertising and Appendix H listing of the substance rather than the rescheduling to Schedule 3 and that it would be useful for XXXX to indicate whether they were comfortable with the concept of rescheduling and their ability to intervene with patients. The Member also stated that it was very difficult with this type of indication to say whether there was a comparable need as there had not previously been a product like this on the market to give pharmacy the opportunity to work with as an over-the-counter substance. The Member felt that this product was an appropriate product for Schedule 3 given the fact that there have been protocols developed around its supply and in recognition of the international experience with the substance as an over-the-counter item. Another Member stated that XXXX were not just opposed to the potential Appendix H listing but that XXXX submissions clearly state that XXXX feel that sumatriptan is a substance which should only be used under medical supervision.

A Member noted that the Committee seemed comfortable with patients who had already been diagnosed and had been given a prescription with accessing the substance through Schedule 3; however the Member also stated that it may be difficult to limit the patient group accessing sumatriptan to these patients.

A Member noted that no-one was suggesting that pharmacists initially diagnose patients with migraines, but that the Committee should consider that patients who have been diagnosed are getting Authority prescriptions with repeats and it is these patients who come in on weekends asking for emergency supply. The Member also stated that it is these patients who must be considered when discussing whether there would be any benefit to supply of sumatriptan as a Schedule 3 substance.

The New Zealand Member stated that there was an unmet clinical need for the substance as a Schedule 3 item in New Zealand. The Member also pointed out that the wording of the New Zealand Schedule 3 entry for sumatriptan does not actually prevent initiation of the substance, rather the wording states “for the treatment of migraine attacks, with or without aura in patients who have a stable, well established pattern of symptoms,” i.e., the wording does not state that the patient has to have had sumatriptan before.

The Committee was informed that emergency supply provisions do exist in New Zealand. The Committee discussed the fact that not all pharmacists would use such provisions and that, if a substance is supplied under emergency supply, the patient will usually be asked fewer questions than if the product was over-the-counter and there was a protocol in

place for supply of the substance. Therefore, there is a patient safety benefit in sumatriptan being available as a Schedule 3 item.

A Member noted that the issue of initiation of therapy is not a new one that the Committee has had to deal with and that is why the label warning of "seek medical advice before first treatment" was introduced. Therefore, Schedule 3 does provide some control and further, that caveats such as specific warnings can be placed on the substance. The Member also raised the point that the labelling and packaging for Schedule 3 substances is designed with information that the consumer can understand.

In summary, the Committee had three issues to consider with regard to the rescheduling of this substance. Firstly – whether this was a condition which required medical management. Secondly – whether this substance had a different safety profile to other substances currently included in Schedule 3, i.e., whether the risk, though rare, of death from side effects changes the Committees view on whether the substance should be available in Schedule 3. Thirdly – whether there is a real supply issue as, ultimately, the primary argument for shifting the substance to Schedule 3 was the supply issue. The Committee agreed that while the first two issues were not insurmountable reasons against down-scheduling, the third issue had not been convincingly argued by either the applicant or any other submission in favour of a Schedule 3 status for sumatriptan.

OUTCOME

Given their concerns surrounding the lack of a real public health need for increased access to the substance through down-scheduling and given the 'emergency supply' provisions already in place, the Committee agreed that the current scheduling of sumatriptan remained appropriate. The Committee noted that this would mean that the scheduling of sumatriptan is not harmonised with New Zealand and that this is appropriate at this time.

12. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS

12.1 SUSDP, PART 4

12.1.1 HYDROCORTISONE 0.5% WITH CINCHOCAINE

PURPOSE

The Committee considered the scheduling of hydrocortisone 0.5% with cinchocaine for rectal use.

BACKGROUND

Hydrocortisone and hydrocortisone acetate were first included in S3 at a concentration of 0.5% or less when present as the only therapeutically active substance at the August 1985 Meeting. The August 1994 NDPSC meeting considered an application that hydrocortisone and cinchocaine preparations for rectal use be rescheduled to Schedule 3.

After due consideration at the May 1995 NDPSC meeting the Committee recommended that the S3 entry for hydrocortisone be amended to allow a topical combination containing cinchocaine for rectal use.

At the February 1999 NDPSC Meeting, hydrocortisone and hydrocortisone acetate (dermal use containing 0.5% or less hydrocortisone in packs containing 30 g or less of such preparation, with no other therapeutically active substance or an antifungal as the only other therapeutically active substance) were included in Schedule 2. The Schedule 3 entry was amended to include specific reference to suppositories. The November 1999 NDPSC Meeting included hydrocortisone in Appendix H of the SUSP, permitting the advertising of hydrocortisone for rectal use.

At the October 2005 NDPSC Meeting, the Committee considered an application for the rescheduling of hydrocortisone acetate (in combination with an anaesthetic) for rectal use from S3 to S2. After discussion, the Committee agreed that the scheduling of hydrocortisone should not be amended due to concerns that consumers may sometimes have difficulty in differentiating between haemorrhoids and other conditions for which the use of a corticosteroid would be inappropriate. Also, concern was expressed that if used on infected skin, there was potential for any infection to be masked or exacerbated. The Committee also expressed concern that the safety data presented as part of the rescheduling application did not truly reflect the safety of the product for anorectal use as it included all adverse events relating to hydrocortisone, regardless of route, dose or duration of treatment.

At the June 2006 NDPSC Meeting, the Committee reconsidered the application to reschedule hydrocortisone acetate (in combination with an anaesthetic) for rectal use. After due consideration of the new safety data presented the Committee agreed that the current scheduling of hydrocortisone and hydrocortisone acetate remained appropriate. Specifically, it was felt that the sponsor had again not adequately justified exactly what advantage there would be to the consumer, should this product be down scheduled and therefore accessed without mandatory intervention of the pharmacist.

At the October 2006 NDPSC Meeting, the Committee considered the outcome of the June 2006 MCC meeting where it was decided that hydrocortisone acetate (in combination with an anaesthetic) should be supplied as a pharmacy only medicine. The Committee considered the MCC's rationale for inclusion of the substances in this schedule and also noted the warning statements which the MCC had applied to the product. After discussion of these issues the Committee agreed to foreshadow

consideration of the scheduling of hydrocortisone 0.5% with cinchocaine for rectal use for the February 2007 Meeting.

DISCUSSION

A submission was received from XXXX requesting rescheduling from Schedule 3 to Schedule 2 for hydrocortisone 0.5% with cinchocaine in rectal preparations. XXXX submission asserted that:

- Haemorrhoids and other anorectal conditions are currently regarded as conditions that are appropriate for self-diagnosis, as is evidenced by the fact that other therapies are already available in Australia without pharmacist supervision. This view is also consistent with the Medicines Classification Committee's recent recommendation in New Zealand to allow XXXX to be sold as a Pharmacy Medicine.
- The proposed rescheduling meets all of the pre-specified criteria detailed in the NDPSC Guidelines for Schedule 2 Medicines. In addition, there are no public health concerns in relation to any of the criteria listed in the NDPSC guidelines.
- XXXX at least as safe and effective as other Schedule 2 treatments for haemorrhoids and other anorectal conditions such as XXXX. A clinical study published in 1988 *(Smith RB and Moodie J. Comparative efficacy and tolerability of two ointment and suppository preparations* XXXX *in the treatment of second degree haemorrhoids in general practice. Curr Med Res Opin 1988; 11(1): 34-40)*, investigated the safety and efficacy of XXXX ointment and suppositories in 39 patients. The authors concluded that 'the present study had confirmed the efficacy and lack of side effects XXXX used for the relief of symptoms associated with second degree haemorrhoids.'
- The risk of systemic toxicity from XXXX is considered unlikely, even when administered in amounts well above the recommended dosage levels. Significant international post-marketing data are available and safety data gathered from this post-marketing data have not revealed any new findings or increased reporting frequency for hydrocortisone and cinchocaine hydrochloride. The majority of the adverse events reported are minor local reactions, which would be easily identified by the consumer and are likely to resolve upon product discontinuation.
- Misdiagnosis by patients who self select XXXX would be unlikely as the majority of patients usually present to a medical practitioner for initial diagnosis. Further, consumer testing had shown the majority of patients XXXX would seek advice from a healthcare professional XXXX, further minimising the likelihood for misuse of the product. Thus, the risk of misdiagnosis occurring is no more than that which currently occurs with other 0.5% hydrocortisone preparations that are already freely available without pharmacist supervision.
- In the small chance that misdiagnosis should occur, use is restricted to seven days unless a doctor had advised the consumer otherwise, thereby ensuring that, medical attention is received and, thus, limiting the product's potential to mask or delay the

diagnosis of any potentially serious medical condition, or compromise the medical management of any other disease.

- The majority of consumers do read and comprehend information contained on packaging and inserts for their OTC medications prior to administering the medication. Also, data had shown that patients who are actually involved in the selection of their OTC medications are significantly more like to understand the information on the product labelling and evaluate the information appropriately.
- The CMI (provided as a package insert) instructs the patient on how to use the product, when the product should not be used, when to stop taking the product, what else should be done i.e. in relation to fluid intake, diet, etc., when to see the doctor and how to store the product. The availability of this document as a package insert provides significant information for the consumer use of XXXX without the direct intervention of a pharmacist.
- There is minimal potential for abuse or misuse of XXXX due to the low toxicity of the active ingredients and the presentation of the product as a suppository or a tube with an applicator. These dosage forms make intentional or accidental misuse extremely unlikely. Thus, XXXX believed the rescheduling of XXXX to Schedule 2 Pharmacy Medicine will not result in any negative public health outcomes in Australia.
- At the June 2006 Meeting, the NPDSC questioned whether haemorrhoids and other anorectal conditions were appropriate for self-diagnosis and self-management. This view is inconsistent with the current availability of Schedule 2 preparations indicated for the treatment of haemorrhoids and other anorectal conditions. The availability of preparations XXXX that can be accessed without mandatory pharmacist intervention, despite the fact that these preparations do not contain hydrocortisone, clearly illustrate that these conditions are currently regarded as self-limiting, short-term disorders which can be successfully and safely self-diagnosed.

XXXX submission proposed the following wording for the hydrocortisone SUSDP entries reflecting XXXX rescheduling request:

Schedule 2

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations containing 0.5% or less of hydrocortisone:

a) for dermal use in packs containing 30g or less of such preparations; and

i. no other therapeutically active substance, or

ii. an antifungal as the only other therapeutically active substance.

HYDROCORTISONE but excluding other salts and derivatives, in preparations containing 0.5% or less of hydrocortisone:

b) for rectal use, when combined when combined with a local anaesthetic but no other therapeutically active substance except unscheduled astringents;

iii. in undivided preparations, in packs of 35g or less, in a quantity of not more than 30 millilitres per container or

iv. in packs containing 12 or less suppositories

The NDPSC evaluation report recommended that the Schedule 2 entry for hydrocortisone be amended to include hydrocortisone combined with a local anaesthetic for rectal use. The following points were highlighted in the report:

- The indication 'for treatment of haemorrhoids or other minor anorectal conditions', met the criteria of a suitable indication for a Schedule 2 product. These are often short-term, self-limited conditions, readily amenable to self-diagnosis. They are often self-treated and very unlikely to be misdiagnosed by the consumer or to mask a serious medical condition. Product usage is simple and likely to be managed appropriately by the majority of consumers even in the absence of advice or counselling. Adequate advice concerning the need for medical attention if symptoms do not respond is provided in the product information. Use of the product is very unlikely to compromise medical management of any other disease.
- Hydrocortisone in topical preparations containing 0.5% or less in a pack size of 30g or less has shown a good safety profile in Schedule 3 use for this indication, with very few reports being made to ADRAC and there is considerable post-marketing experience, both within Australia and overseas. The spontaneous reporting rate of adverse events has been very low and post-marketing surveillance, both by ADRAC and via reports to the sponsor, indicated that the topical preparation is very safe in over the counter use. There is no evidence that this combination should be any less safe than other products for minor anorectal conditions that are currently included in Schedule 2.
- Dermal tolerability is reasonable and reactions are mild. Systemic absorption following topical administration of low doses is likely to be minor. Since the total dose of hydrocortisone contained in the pack is 150mg for the ointment and 60mg for the suppositories, even the oral ingestion of the entire contents of the pack would be very unlikely to cause acute toxicity in either adults or children. There were no concerns in relation to abuse potential or drug interactions.

- The public health arguments had been adequately addressed in the submission, and the NPDSC's previous considerations. A major argument from the sponsor was that consumers would be more likely to seek the product if it was available under Schedule 2 than Schedule 3 because of embarrassment about approaching a pharmacist. Given that the suppository formulation requires refrigeration, consumers would still be required to approach a pharmacy assistant and the potential for embarrassment appears likely to be similar. However, there are no public health concerns in relation to any of the criteria listed in the NDPSC guidelines.
- The Medicines Classification Committee in New Zealand had recommended that the combination of hydrocortisone 0.5% with local anaesthetic for anorectal use in small quantities should be available as a Pharmacy-only medicine (equivalent to Schedule 2) and has recommended that the NDPSC should be asked to harmonise on this recommendation. The warnings recommended by the MCC in relation to use in children, recurrent use, and need for medical advice if the condition persists or if there is rectal bleeding have been included in the proposed consumer product information.

The evaluator recommended the following Schedule 2 entries:

> HYDROCORTISONE AND HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations containing 0.5 per cent or less hydrocortisone fro dermal use in packs containing 30 g or less of such preparations containing:
>
> (a) no other therapeutically active substance; or
>
> (b) an antifungal as the only other therapeutically active substance

and

> HYDROCORTISONE but excluding other salts and derivatives, in preparations containing 0.5 per cent or less of hydrocortisone for rectal use when combined with a local anaesthetic but no other therapeutically active substance except unscheduled astringents:
>
> (a) in undivided preparations, in packs of 35 g or less, in a quantity of not more than 30 millilitres per container; or
>
> (b) in packs containing 12 or less suppositories

XXXX did not provide a pre-meeting response.

XXXX provided submissions in which XXXX stated that XXXX had no objection to the rescheduling of hydrocortisone with cinchocaine for rectal use from Schedule 3 to Schedule 2.

XXXX provided a submission in which XXXX supported the rescheduling of hydrocortisone with cinchocaine for rectal use from Schedule 3 to Schedule 2 as this would be in line with the principals of trans-Tasman harmonisation and the Council of Australian Governments (CoAG) statements in relation to minimum effective regulation.

XXXX provided a submission in which XXXX opposed the rescheduling of hydrocortisone with cinchocaine for rectal use from Schedule 3 to Schedule 2. XXXX main points were:

- The most common side effect of hydrocortisone is skin thinning and atrophy as well as possible interference with local flora which may lead to opportunistic infection. Excessive application of local anaesthetics to the rectal mucosa should be avoided as absorption and sensitisation of the anal skin can occur.
- It is important that perianal symptoms not responding to treatment be assessed by a health professional, as, while they may be associated with haemorrhoids, they may be the result of a more serious condition such as psoriasis, carcinomas, diabetes or sexually transmitted disease.
- XXXX noted that the NDPSC Guidelines describe a Schedule 2 substance as one which is used for minor ailments which are easily recognised by the consumer and which do not require medical diagnosis or management. They must also have a low risk of masking a serious disease. XXXX also noted that the Guidelines for Schedule 3 substances require counselling or advice from a pharmacist and are for ailments where the risk of masking a serious condition can be managed by the pharmacist.
- XXXX believed that rectal hydrocortisone products should be placed in Schedule 3 of the SUSDP. While consumers easily recognise the symptoms of haemorrhoids they can not tell whether they could be reflecting a more serious condition. Mandatory pharmacist intervention allows for questioning regarding additional symptoms, treatment history and oversight of supply. As a Schedule 2 medicine, because of the embarrassing nature of the condition, consumers would be more likely to self select and self treat without seeking out healthcare advice.
- XXXX noted that placement of a substance in Schedule 2, in every jurisdiction bar Queensland and Western Australia, means that the consumer can self select the item without the need to consult any staff member at all. Including this substance in Schedule 2 may increase the risk of patients treating more serious conditions without attempting (due to embarrassment) to obtain advice. This in turn increases the risk of misdiagnosis, masking of a more serious condition and unsuccessful/ unsuitable treatment.

XXXX noted that currently there are available unscheduled astringent/ emollient products which are suitable for the treatment of minor peri-anal conditions. There is no substantial benefit to rescheduling hydrocortisone preparations; indeed there is an increased risk to consumers of these products being misused to treat conditions which are more serious than haemorrhoids.

A Member noted that the concerns regarding the safety of the product could be dealt with by appropriate labelling directing the patient to seek medical advice if symptoms do not clear within a defined time and that the conditions being treated fell within the guidelines for treatment with a Schedule 2 substance. The Member also noted that the product had been available as a Schedule 3 item for a number of years and that there had been no recorded issues of skin thinning or other serious adverse events with the substances. Members also noted that similar preparations were available as Schedule 2 or equivalent in a number of overseas markets.

Members discussed the proposed wording of the Schedule 2 entry relating to the pack size of the product. Members noted that the proposed wording of the Schedule 2 entry reflected that in the New Zealand schedules and that, therefore, the Australian and New Zealand entries would be harmonised if this wording was used.

DECISION 2007/49 – 21

The Committee agreed to amend the scheduling of hydrocortisone in combination with an anaesthetic for rectal use from Schedule 3 to Schedule 2 as the NDPSC guidelines for inclusion as a Schedule 2 substance were met. The Committee noted that this would also harmonise scheduling of the substances with New Zealand.

Schedule 2 – Amendment

HYDROCORTISONE AND HYDROCORTISONE ACETATE – amend entry to read:

HYDROCORTISONE AND HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations containing 0.5 per cent or less hydrocortisone:

(a) for dermal use in packs containing 30 g or less of such preparations; and

(i) Containing no other therapeutically active substance; or

(ii) an antifungal as the only other therapeutically active substance; or

(b) for rectal use, when combined with a local anaesthetic but no other therapeutically active substance **except** unscheduled astringents:

(i) in undivided preparation, in packs of 35 g or less; or

(ii) in packs containing 12 or less suppositories.

Schedule 3 – Amendment
HYDROCORTISONE AND HYDROCORTISONE ACETATE – amend entry to read:

HYDROCORTISONE AND HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations containing 1 per cent or less of hydrocortisone:

(a) for dermal use, in packs containing 30 g or less of such preparations; and

(i) containing no other therapeutically active substance; or

(ii) containing an antifungal but no other therapeutically active substance; or

(b) for rectal use, when combined with a local anaesthetic but no other therapeutically active substance **except** unscheduled astringents:

(i) in undivided preparations, in packs of 35 grams or less; or

(ii) in packs containing 12 or less suppositories,

except when included in Schedule 2.

12.1.2 RANITIDINE

PURPOSE

The Committee considered the scheduling of ranitidine.

BACKGROUND

Ranitidine is a member of the class of histamine H_2-receptor antagonists with antacid activity. Ranitidine is a competitive and reversible inhibitor of the action of histamine, released by enterochromaffin-like (ECL) cells, at the histamine H_2-receptors on parietal cells in the stomach, thereby inhibiting the normal and meal-stimulated secretion of stomach acids. It is used where inhibition of gastric acid secretion may be beneficial, as in peptic ulcer disease, including stress ulceration, gastro-oesophageal reflux disease, selected cases of persistent dyspepsia, pathological hypersecretory states such as the Zollinger-Ellison syndrome, and in patients at risk of acid aspiration during general anaesthesia or child birth.

Ranitidine was first considered by the DPSSC at its May 1982 Meeting in response to an approval for registration granted by the ADEC at its 101st Meeting in December 1981. At this Meeting the Committee recommended the inclusion of a new entry for ranitidine in Schedule 4 of the SUSDP.

At its May 1988 Meeting, the DPSSC considered an application to reschedule ranitidine in packs of no more than 10 dosage units to Schedule 3 from Schedule 4. At this meeting the Committee discussed the data presented and reaffirmed, based on safety considerations, that Schedule 4 was the correct Schedule for this substance.

The November 1993 Meeting of the DPSSC considered an application to down schedule small packs of H_2- receptor antagonists from Schedule 4 to Schedule 3. Ranitidine was one of the substances that the Committee discussed. The Committee considered the scheduling status of this substance around the world and the restrictions that would be placed on the substance for OTC supply, taking into particular account the proposed New Zealand scheduling. The Committee considered that these restrictions would ensure that criteria for inclusion in S3 were met and concerns regarding the safety of OTC supply of this substance allayed. The Committee drafted a number of warning statements for use on the OTC packaging for this substance. The Committee also considered limiting the period of OTC supply would also be a sufficient means of limiting duration of use. The Committee considered that 14 days supply would be appropriate for OTC use. Thus the Committee agreed to foreshadow recommendation of inclusion of ranitidine 150mg or less per dosage unit in Schedule 3 for a maximum of 14 days supply when labelled with the appropriate warning statements.

At the April 1994 NDPSC Meeting, the Committee considered a submission from the sponsor company regarding the proposed warning labelling of ranitidine. The Committee

noted that advice on the warning statements had been referred to XXXX XXXX for comment on any potential public health issues, but that comment had not been received as yet. In view of this need for clarification before a final recommendation was able to be made, the Committee recommended that its decision from the November 1993 meeting be maintained until further advice was received.

The August 1994 NDPSC Meeting considered an application from XXXX to reschedule ranitidine 150mg from Schedule 4 to Schedule 3 in packs containing 15 doses or less when used for the treatment of heartburn and other symptoms of reflux oesophagitis. The Committee considered that the wording proposed by the applicant for the schedule entries was not consistent with the requirement for S3 inclusion that the substance be used for relief of minor and temporary ailments as it contained indications which would have to be approved by TGA. The Committee recommended that companies be advised to have any indications approved by the TGA. The Committee also discussed potential warning statements and finalised the wording for them.

The Committee further considered the issue of down scheduling ranitidine from S4 to S3 at its February 1995 Meeting. At this meeting the Committee reaffirmed its original foreshadowed decision from the November 1993 Meeting to include 150mg or less of ranitidine in Schedule 3 when in a pack containing not more than 14 days supply and when labelled with certain warning statements.

At the November 1996 NDPSC Meeting, the Committee agreed to remove the restriction applying to dosage size in the Schedule 3 entry for ranitidine. The Schedule 3 entry was amended to reflect this decision.

At its August 1998 Meeting, the Committee considered an application to include ranitidine in Appendix H of the SUSDP. Following discussion of the data supplied and whether there were any particular safety concerns arising from the advertising of ranitidine, the Committee agreed to include a new entry for ranitidine in Appendix H.

At the November 2000 Meeting of the NDPSC, the Committee considered a submission to reschedule ranitidine from Schedule 3 to Schedule 2. The Committee considered the data presented in the submission as well as pre-meeting comments from a number of sources. The Committee discussed the safety profile of ranitidine, including the potential for ranitidine to mask more serious, underlying conditions. The Committee also noted that the indications for the substance were appropriate for a Schedule 2 classification and that the warning statements clearly advised the consumer that the use of the product was for short-term treatment only. Following consideration of the above issues, the Committee agreed to the inclusion of a new entry in Schedule 2, with retention of Appendix F warning statements, for ranitidine when supplied in packs containing no more than 14 days supply.

At the June 2002 NDPSC Meeting, the Committee considered a submission requesting the exempting of ranitidine from warning statements 68 (if symptoms persist beyond 5

days consult a doctor), 39 (This medicine may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol) and 70 (Use only under medical supervision of you are taking other medicines) in the SUSDP. After consideration of the wording of the current warning statements, the Committee agreed to foreshadow amendment to the Appendix F entry for ranitidine to simplify and clarify the warning statements. At the October 2002 meeting, amended wording to what was proposed by the Committee was received from MEC. The Committee discussed this amendment and agreed that it was consistent with the intent of the warning statements adopted by New Zealand. The Committee agreed to amend the warning statement for ranitidine on the basis that it would convey clear directions to consumers.

At the February 2005 NDPSC Meeting, the Committee agreed to foreshadow removal the indication "gastro-oesophageal reflux" from the S2 entry in order to be harmonised with New Zealand on this substance. This recommendation was confirmed at the July 2005 NDPSC Meeting.

DISCUSSION

A submission was received from XXXX requesting rescheduling from Schedule 2 to exempt from Scheduling for ranitidine 150mg, with a maximum dose of 300 mg/day, for the effective long lasting relief of heartburn and acid indigestion in packs containing no more than 7 days supply. XXXX submission asserted that:

- Ranitidine is already available as an unscheduled product in a number of markets including the USA (approved for OTC, equivalent to unscheduled, at 150mg in 2004), Canada (at 75mg since 1998) and the UK (a maximum pack size of 12 tablets and a maximum daily dose of 150mg). Other H_2-antagonists, famotidine and nizatidine, are also available as unscheduled medicines in the USA and as OTC medicines in Canada and the UK as well as Australia. Thus, XXXX proposal to classify ranitidine 150mg for a maximum of 7 days supply to unscheduled status is in line with its availability in other comparable markets.
- Heartburn and other symptoms of indigestion related to gastric hyperacidity, such as indigestion and acid indigestion, are extremely common, with data suggesting that up to 7% of people suffer from heartburn daily, 13% once a week and 24% at least once a month. A 1996 survey conducted in Australia found that 56% of respondents reported that they had suffered from heartburn at some time in the past and 37% had symptoms at least once every 4-6 months. The data also showed that the incidence of episodes increased with age and was more common in men than women and that over half of these patients were likely to use an antacid to treat their symptoms while 20% used prescription medications. Current market share data showed that antacids were the most widely used products to relieve the symptoms of gastro-oesophageal reflux, accounting for approximately 70% of the Australian heartburn and indigestion market.

- Currently antacid/ alginate products are the only substances available in the unscheduled environment in Australia. However, despite their widespread use, it is noteworthy that in recent systematic reviews investigating pharmacological interventions for non-ulcer dyspepsia, antacids were found to be no more effective than placebo. In contrast, 11 eligible trials with H_2 antagonists were reviewed and these results were statistically significant compared to placebo. Moreover, although they are generally well tolerated, antacids do have the potential to cause side effects in susceptible patients. However, despite this well-documented adverse event profile, most individuals use these products in an unsupervised general sale environment with apparently few reported problems. Thus, there appears to be a need for broader access to a more effective, longer lasting and safer alternative for the treatment of heartburn and related symptoms.
- A review of data from 189 controlled clinical trials as well as analyses of post-marketing surveillance studies and spontaneously reported adverse events has confirmed the excellent safety profile of ranitidine. Further, there are no clinically significant interactions between ranitidine and commonly prescribed medications. There has been extensive experience with millions of people using ranitidine as a non-prescription product over the last 12 years. In the period July 2005 to May 2006, it is estimated that patient exposure to ranitidine tablets was 1.1 billion treatment days. In addition, 78 million ampoules of injectable ranitidine, 224 million millilitres of ranitidine syrup, and 100 million ranitidine 75mg OTC tablets were sold during the time period. During this time, 218 serious and non-serious reports have been received worldwide.
- The National Prescribing Service recommends H_2 receptor antagonists as the first line treatment in a step-up approach to managing the symptoms of dyspepsia. The availability of ranitidine in single doses of 150mg, in pack sizes limited to a maximum of 7 days supply (equivalent to pack sizes currently marketed for antacids in the general sales environment) as an unscheduled product would meet the current need for greater access to a more efficacious, longer lasting and safer medication with which to relieve the symptoms of heartburn and indigestion.
- Numerous controlled studies have proven that ranitidine can be safely co-administered with other drugs, with co-administration with warfarin being the main potential interaction. However, antacids interact with many prescription drugs, the most significant being with warfarin, lithium, iron, digoxin, certain antibiotics and enteric-coated tablets of any medicine.
- The available data indicated that, in the decade that ranitidine has been available as a non-prescription product; there is limited evidence of abuse or overuse of this product. Further, data obtained by XXXX demonstrated that the potential unscheduled availability of products to treat heartburn and indigestion is independent of consultation behaviour. Thus, appropriately labelled H_2 antagonist product in the general sales environment accompanied by good supporting educational information would likely help to direct more consumers to seek advice when such products do not

relieve their symptoms. This may present a more balanced approach to self-care and the quality use of medicines than the current situation in which antacids are effectively viewed as commodity products.

- There is no evidence that ranitidine has any euphoric effect or any potential for abuse.

XXXX submission proposed the following wording for the ranitidine SUSDP entries reflecting XXXX rescheduling request:

> **Schedule 2**
>
> RANITIDINE when sold in the manufacturer's original pack containing no more than 14 days supply **except** ranitidine 150mg when sold in the manufacturer's original pack containing not more than 7 days supply.

The NDPSC evaluation report recommended that ranitidine 150mg tablets should be exempt from Scheduling when supplied in packs containing no more than 7 days supply. The following points were highlighted in the report:

- Ranitidine is a specific antagonist of H_2 receptors and its major therapeutic effect is the inhibition of gastric acid secretion. It is used in the management of dyspepsia, gastric ulcer and reflux oesophagitis, and has an excellent safety record with very few adverse effects, a very wide therapeutic index and as it has no psychotropic effects a very low potential for abuse/ misuse. AE reporting rates in clinical trials were similar to that of placebo and there has been a very low reporting rate in post-marketing surveillance. Advice or counselling is not required for the safe use of ranitidine. Ranitidine is also not subject to clinically significant interactions with commonly used substances or food.
- The indication "relief or treatment of indigestion/heartburn/reflux" is already accepted as an appropriate indication for listed, unscheduled products including antacids, and is therefore already regarded as suitable for self management in an unscheduled environment. The symptoms being treated are generally minor and unrelated to serious conditions, although occasionally they may indicate the presence of a serious condition such as a peptic ulcer or severe gastro-oesophageal reflux disease. However, lack of response to an unscheduled medicine, including an H_2 antagonist is likely to lead to consultation with a doctor, and this approach is advised in the package information for consumers.
- Dyspepsia is very common and very rarely a symptom of serious disease. The suppression of symptoms of a serious underlying disease for a brief period is a possibility, but the pack size makes the potential for adverse consequences very low. In the case of the proposed pack for general sales, there will be advice provided that consumers should not exceed one week of continuous treatment without seeking advice from their medical practitioner. The risk of masking a serious disease, which

would cause persistent symptoms, is likely to be little more than would be observed with antacids.

- There is considerable OTC marketing experience in Australia (currently S2) as well as in the USA, UK, and Canada, some of this in the unscheduled environment. No significant problems have been encountered in relation to unscheduled use. Inappropriate use of the proposed product would be limited by the small pack size XXXX and safety data are available from clinical trials including dose levels of 1200mg/day, and from reported overdoses of up to 18g which support the very high degree of safety of ranitidine. Ingestion of the total dose included in the proposed pack XXXX would be very unlikely to lead to serious outcomes.
- The arguments for unscheduled availability, as opposed to Schedule 2 availability, are reasonable and consist largely of the need for a more effective and longer-lasting remedy for intermittent dyspepsia than is currently available (predominantly antacids, which do not have a better efficacy or safety profile than ranitidine).
- The sponsor made a reasonable argument that the availability of ranitidine in the grocery environment is likely to provide more benefit to consumers and cause fewer problems than antacids. There are no significant public health issues in relation to the purpose of use, the way in which it is to be used, the dosage form, extent and pattern of use, misuse, interactions or bioaccumulation. The proposed package type and size reduces the possibility of childhood poisoning, which is very unlikely in any event, given the very wide therapeutic index of ranitidine. The proposed labelling would also advise against use in pregnancy, although the evidence suggests that the risk of malformations is very low.

The evaluator recommended the following Schedule 2 and 4 entries:

Schedule 2

RANITIDINE in solid dosage forms of 150mg when sold in the manufacturer's original pack containing not more than 28 units **except** when sold in the manufacturer's original pack containing not more than 14 units

Schedule 4

RANITIDINE except when included in or expressly excluded from Schedule 2

XXXX provided a pre-meeting response to the NDPSC evaluator's report. XXXX main points were:

- The rescheduling proposal for ranitidine is in line with the current Schedule 2 entry for ranitidine which does not limit the S2 availability of ranitidine to solid dose forms, unlike the NDPSC evaluators' recommendation for the unscheduled presentation. The key principal in the proposal is limiting the number of days supply, not the dosage

form to solid. The safety data presented in the application relates to all dosage forms of ranitidine, not just the solid.

- In Australia and New Zealand ranitidine is currently supplied at both 150mg and 300mg as an S2 substance as the current entry allows. XXXX as the current S2 entry allows for all oral dosage forms, not just solid.
- It was XXXX opinion that the evaluators' recommendation to redraft the S2 entry for ranitidine to limit availability to 150mg solid dosage form products was not retaining the same effects as the current Schedule entry and would unwittingly result in the up scheduling of the 300mg dose and all oral preparations other than solid to Schedule 4, i.e., it would make the current S2 entry more restrictive. This was not the intention of the rescheduling proposal and to XXXX knowledge there were no safety or public health concerns to warrant such an action.
- XXXX reinforced that the current proposal to reschedule ranitidine to unscheduled status supports the proposed amendment of the S2 schedule entry for ranitidine:

  Schedule 2 [current entry]

  RANITIDINE when sold in the manufacturers original pack containing no more than 14 days

  Schedule 2 [proposed entry]

  RANITIDINE when sold in the manufacturers original pack containing no more than 14 days supply **except** RANITIDINE 150mg when sold in the manufacturers original pack containing no more than 7 days supply.

- In essence the proposed entry was retaining the same effect as the current S2 entry, the only difference being that it allowed for the exemption of a certain dose and pack size.
- XXXX stated that this proposal was in line with Quality Use of Medicines principals and in accordance with the current S2 entry for ranitidine which permits the availability of 300mg single dose ranitidine as well as solid and liquid dose forms.

XXXX provided a submission in which XXXX stated that:

- Although ranitidine has a well established safety profile and low drug interaction potential, the exemption from scheduling for this substance would lead to an absence of in-store advice for people who take the drug continuously and thus may be masking a serious underlying condition. Also, as there would be no restrictions on the sale of multiple packets potentially resulting in substances being taken for prolonged periods without appropriate advice or intervention being available.
- XXXX also stated that Australia should be wary of a "step-by-step" deregulatory process which would bring the supply of non-prescription pharmaceutical items in

Australia into line with the USA as this would undermine Quality Use of Medicine policy.

XXXX provided submissions in which XXXX stated that XXXX were opposed to the exemption from scheduling for ranitidine. XXXX main points were:

- There is concern that the exemption would allow supply of the substance without access to the advice of a pharmacist, which in the case of patients taking the substance continuously, means that a serious underlying condition may be masked.
- Given this serious risk and having regard to the Quality Use of Medicines policy XXXX XXXX opposed the exemption proposal.

XXXX provided a submission opposing the proposal to exempt ranitidine from scheduling. XXXX main points were:

- While heartburn and indigestion are common presentations in pharmacies these symptoms can also be indicative of an underlying, more serious condition.
- Provision of OTC treatments for these symptoms is guided by careful history taking by pharmacists and patients who present with more serious or more frequent, non-resolving symptoms are referred to their doctor without any treatment being supplied. XXXX believed that without this opportunity for discussion and possible referral patients may continue taking inappropriate treatments which may delay them seeking proper medical attention.
- XXXX believed that ranitidine should remain Schedule 2 substance so as consumers still have this opportunity to seek information and advice from their pharmacist regarding the use of this product.

XXXX provided a submission opposing the proposal to exempt ranitidine from scheduling. XXXX main points were:

- The treatment algorithm for gastro-oesophageal reflux disease (GORD) is not well understood by consumers and some doctors which is evidenced by the over prescribing of proton pump inhibitors and lack of understanding of alginate products. This over prescribing results in a significant economic burden.
- XXXX stated that until the treatment of GORD is based on a better understood and widely adopted algorithm, it would be premature to reclassify ranitidine. With its current classification there is opportunity for intervention of pharmacy staff in the sale and this provides the opening for patient education on the matter.

XXXX provided a submission opposing the proposal to exempt ranitidine from scheduling. XXXX main points were:

- XXXX noted that the Guidelines describe a Schedule 2 substance as one which is substantially safe in use but for which counselling is available if needed and that the substance has a low risk of masking a serious disease and a low potential for harm.

Although unscheduled medicines are not defined within the Guidelines, the assumption is that they are safer and have lower risk than Schedule 2 medicines.

- XXXX had concerns that the non-prescription supply of ranitidine had the potential to mask serious conditions such as gastric cancer. XXXX also suggested that these products may cause indirect harm by masking the adverse events of other common medicines which are exempt from scheduling such as ibuprofen, aspirin or nicotine-replacement-therapies (NRT).
- XXXX also had concerns regarding the increasing availability of H2 antagonists to the elderly without the opportunity for intervention by a healthcare provider. XXXX quoted a US study which showed that many of the elderly self treat with H2 antagonists for reflux but that the complications of this can involve severe respiratory problems (uncontrolled asthma, aspiration pneumonia etc). Keeping ranitidine as a Schedule 2 substance would give these patients the opportunity to seek advice if required.
- Pharmacies are required to have procedures and protocols in place which facilitate trained staff to interact with consumers seeking Schedule 2 substances, particularly with regards to multiple pack or regular repeat sales. This is not required for non-pharmacy retail outlets which sell exempt substances. This means that medicines which are exempt from scheduling should be associated with virtually nil risk of masking serious conditions, which is not the case for ranitidine.
- The general assumption with the currently available exempt from scheduling antacids is that appropriate labelling of these products will allow consumers with chronic problems to recognise that continual regular dosing requirements (every few hours) is an indication that they should see a healthcare professional. Ranitidine, however requires dosing only twice daily and the better control and less frequent dosing this provides may reduce the significance of a chronic condition to a consumer and, thus facilitate self treatment rather than seeking professional advice.
- Although the current proposal restricts supply to 7 days, there is no restriction on the number of packs that can be purchased at any one time from non-pharmacy outlets and the Committee had previously shown its concern that this substance may be used to mask more serious conditions by restricting the Schedule 2 pack size. Pharmacy could offer the controls to ensure that, even though the public has increased access to Schedule 2 medicines, their use is in line with Quality Use of Medicines principles.
- XXXX also mentioned XXXX concerns regarding the ready availability of NSAIDs through non-retail outlets and the risk these substances have with regard to producing gastric problems. XXXX noted XXXX concern that ranitidine could be used by consumers to treat the adverse events caused by these other substances and, thus, mask more serious health outcomes. XXXX also felt that the lack of controls on the marketing of exempt substances may lead to ranitidine being actively promoted for reflux in campaigns juxtaposed to campaigns for substances such as NSAIDs.

- XXXX noted that in pharmacy a consumer presenting to a sales counter with both an NSAID or an NRT and an H_2 receptor antagonist would flag to pharmacy staff that pharmacist intervention would be required.
- XXXX contended that there were serious concerns with the potential of ranitidine to mask more serious conditions or adverse events of other medications which can have a significant effect on public health. Thus, XXXX believed that ranitidine was more suited to a Schedule 2 classification.

A Member also noted that ranitidine was a widely used product at the general sales level in a number of countries and that the concerns (such as masking a serious disease, interactions with other substances) the Committee stated in response to the initial submission to reschedule ranitidine from Schedule 4 to Schedule 3, have not been realised in the ten years this substance has been available as a Schedule 3 or 2 item. Members discussed that there was no safety reason why an appropriately labelled pack should not be available as a general sale item as the sponsor had provided evidence from two studies that showed that approximately 80% of patients can and do read labels and follow instructions. A Member noted that the current CMI would be amended slightly to reflect the general sales status of the substance and provided with the general sales pack. The Member also noted that even if patients did not follow the label instructions that there was little risk from toxicity given the small size of the proposed general sales pack and that the issue was that there be strong enough warnings to the patient that they should seek medical advice if they had any particularly listed symptoms and that this advice was currently in the CMI. Another member noted that there were no emerging safety issue for the substance as an S2 substance; therefore there would be no concern with it becoming a general sale item.

Members discussed the suggestion by the evaluator to limit the Schedule 2 entry to solid dosage forms only. A Member noted that the current Schedule 2 entry does not place a restriction on dosage form, that the sponsor was not requesting this change and that there was no rationale for amending the Schedule 2 entry to exclude liquid dosage forms. Members discussed the XXXX response to the evaluators suggested wording for the Schedule 2 entry and that there is no current restriction to dose form in the Schedule 2 entry. Members discussed whether there were any liquid dosage forms currently available in Australia. A member noted that there was currently an oral liquid product available in Australia. Members discussed concerns regarding the liquid dosage from being mainly for paediatric use and that with other, unscheduled liquid antacids XXXX that people just swig from the bottle and do not take the correct, measured dose of them. A Member stated that it is the perception with these substances that they are completely safe and that there was concern that people may treat liquid ranitidine in the same way.

Members went on to discuss whether the exemption from scheduling should be limited to solid dosage forms or whether it should include all dosage forms. Members agreed that due to the potential for liquid dosage forms to be more easily accessed by children and

their potential for inappropriate use to limit the exemption from scheduling to solid dosage forms only.

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Due to its established safety profile, the safety information provided on the package label and in the CMI being adequate and that the indication is an accepted indication for unscheduled products, the Committee agreed to amend the scheduling of ranitidine when sold in solid dosage forms in manufacturer's original pack containing not more than 7 days supply with a maximum dose of 300 mg per day from Schedule 2 to exempt from scheduling. The Committee agreed to refer the matter to the Drafting Advisory Panel to fine tune the wording of the schedule entries.

Schedule 2 – Amendment

RANITIDINE – Amend entry to read:

RANITIDINE in preparations supplied in the manufacturer's original pack containing not more than 14 days supply **except** when supplied as divided preparations for oral use containing 150mg or less of ranitidine per dosage unit in the manufacturer's original pack containing not more than 7 days supply.

Schedule 4 – Amendment

RANITIDINE – Amend entry to read:

RANITIDINE **except**:

(a) when included in Schedule 2; or

(b) in preparations supplied in the manufacturer's original pack in divided preparations for oral use containing 150mg or less of ranitidine per dosage unit containing not more than 7 days supply.

12.1.3 BENZYDAMINE

PURPOSE

The Committee considered the scheduling of benzydamine for dermal use.

BACKGROUND

Benzydamine hydrochloride is an indazole non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic, and anti-oedema properties. Unlike other NSAIDs,

benzydamine hydrochloride does not inhibit cyclooxygenases (COX) but stabilizes membranes, resulting in local anaesthesia. It inhibits the production of pro-inflammatory cytokines as well as inhibiting the generation of reactive oxygen species by neutrophils, leukocyte aggregation and adhesion and it also exhibits antimicrobial properties. It is used to reduce post-surgical and post-traumatic pain and oedema and to promote healing. It is also used topically in treatment of rheumatic diseases and inflammation of the mouth and throat.

Benzydamine was first considered by the DPSSC at its November 1969 Meeting where the Committee recommended the inclusion of a new entry (Benzydamine HCl) in Schedule 4.

At its November 1986 Meeting, the DPSSC considered an application for rescheduling of topical benzydamine to Schedule 2. This was considered in response to the approval by ADEC XXXX at its 123rd meeting in April 1986. At this meeting the Committee agreed to a new Schedule 2 entry for benzydamine in preparations for topical use containing 3% or less of benzydamine.

At the February 1999 NDPSC Meeting, the Committee considered an application to down-schedule 5% topical benzydamine from Schedule 4 to Schedule 2. The Committee considered the safety profile of the 5% cream compared to the 3% cream and found there to be no difference between the two preparations. Based on this, and the principles of Trans Tasman Harmonisation, the Committee decided to amend the Schedule 2 entry for benzydamine to benzydamine in preparations for topical use.

DISCUSSION

A submission was received from XXXX requesting the rescheduling from Schedule 2 to exempt from scheduling for benzydamine in dermal use preparations. XXXX submission asserts that:

- Dermal benzydamine preparations have been available as OTC medicines since 1980 and were the first of the NSAID class to be made Schedule 2 in 1987 and there had been no evidence of increased risk to consumers with the availability of these preparations.
- Other NSAIDs for dermal use have already been exempted from scheduling (i.e. ibuprofen, diclofenac, ketoprofen and piroxicam) and dermal preparations of benzydamine have a comparable risk/ benefit ratio to ibuprofen, diclofenac and piroxicam.
- Since 1997, fifteen reports of adverse reactions have been received by ADRAC and these have mainly been application site reactions. On report related to an irritated, bleeding mouth due to incorrect use of the dermal product and two reports related to taste perversion and dizziness.

- Approximately 95% of topical benzydamine has a localised action with a relative systemic bioavailability of around 5%. Benzydamine has been detected in blood and urine following single applications of benzydamine cream. A total of 3% of the dose was excreted in the urine over 72 hours compared with 10% of the dose over 24 hours following oral administration.
- A large meta-analysis of 86 placebo controlled clinical studies of dermal NSAIDs in acute painful conditions such as soft tissue injuries, strains and sprains provided evidence that externally-applied nonsteroidal anti-inflammatory agents, including benzydamine, were significantly better than placebo over 1 week, with the number needed to treat (NNT) for all NSAIDs in these conditions of XXXX The review also showed that the level of adverse events and withdrawals from the trial were no different from the placebo group.
- That the current XXXX Schedule 2 pack clearly identifies what a consumer needs to know to appropriately self-select a topical dermal anti-inflammatory product. It is proposed to only remove the signal heading from the S2 pack for the unscheduled pack. The layout of the label would be structured in such a way that consumers can readily identify how to use the product, the situations when it should not be used and what to do if skin reactions occur.
- Benzydamine meets the criteria for a preparation to be exempted from scheduling in that the indications are for minor ailments or symptoms capable of being easily recognised and self-treated by the consumer, it has an acceptable safety profile and a low or absent potential for abuse or inappropriate use.

XXXX submission proposed the following wording for the benzydamine SUSDP entries reflecting XXXX rescheduling request:

> **Schedule 4**
> BENZYDAMINE **except** when included in Schedule 2
>
> **Schedule 2**
> BENZYDAMINE in preparations for topical use, **except**
> (a) in preparations for dermal use

The NDPSC evaluation report recommended that benzydamine for dermal use be exempt from scheduling. The following points were highlighted in the report:

- Dermal benzydamine preparations have been available as OTC medicines since 1980, and were the first NSAID class to be switched to Schedule 2 in 1987. Since then a number of other NSAID products for dermal use have been exempted from scheduling.

- XXXX cream and gel formulations are currently indicated for the temporary relief of pain and inflammation in muscles and joints and the cautionary statements for use are appropriate and in accord with other similar preparations.
- Benzydamine cream and gel preparations with the identical formulation of XXXX cream and gel have been approved in a number of different countries worldwide since 1980 and in many of these countries the formulations are available in non-pharmacy outlets. Thus there is significant post-marketing experience with these products.
- 106 adverse drug reaction reports have been made to ADRAC for dermal benzydamine products since 1987 and 15 reports have been made since 1997. The major reactions include rash, bullous eruption or other application site reactions. Although the total adverse drug reaction events are greater for XXXX cream and gel versus other topical NSAIDs, it should be noted that this product was available earlier than the alternative products (i.e., 1987 and 1990 for XXXX cream and gel compared to 1994 – 2002 for the other agents).
- Global consumer reports from the PSUR for XXXX show a total of 211 case reports for a patient exposure of 132 million patient years. A review of XXXX clinical trials involving XXXX patients and a number of different NSAID agents showed at least a 50% reduction in pain compared to placebo and local and systemic AEs and drug related withdrawals were no different for those in treatment to those in placebo groups.
- XXXX did not provide a pre-meeting response.

XXXX provided submissions in which XXXX stated that they had no objection to exempting preparations of benzydamine for dermal use from scheduling.

Members noted that the safety profile of benzydamine from ADRAC reports correlated with that from the clinical trial data presented by the sponsor. Members also noted that there were many other topical NSAID agents that were unscheduled and that the levels of ADRs seen with benzydamine was similar to that with these other agents.

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The Committee agreed to exempt benzydamine for dermal use from scheduling given its indications for use and safety profile.

Schedule 2 – Amendment

BENZYDAMINE – Amend entry to read:

BENZYDAMINE in preparations for topical use, **except** in preparations for dermal use.

Schedule 4 – Amendment

BENZYDAMINE – Amend entry to read:

BENZYDAMINE **except:**

(a) when included in Schedule 2; or

(b) in preparations for dermal use.

12.1.4 CLOTRIMAZOLE

PURPOSE

The Committee considered the scheduling of clotrimazole for vaginal use.

BACKGROUND

Clotrimazole is an antimycotic drug with activity against *Candida albicans*, and lesser activity against other species of *Candida*. Currently it is marketed in over 100 countries under various trade names. It is registered in Australia for several indications, including topical vaginal use for the treatment of vaginal candidiasis.

The August 1977 DPSSC Meeting included clotrimazole in Schedule 4. At the April 1994 NDPSC Meeting the Committee agreed to down-schedule preparations of clotrimazole for vaginal use to Schedule 3 to give the current entry. Following out-of-session consideration the Committee also agreed to include the current warning statements in Appendix F for clotrimazole when included in Schedule 3.

At the November 1996 NDPSC Meeting the Committee considered a submission from XXXX requesting the rescheduling of clotrimazole for vaginal use to Schedule 2. The Committee did not support the rescheduling application. Post-meeting comment concerning the November 1996 decision was considered at the February 1997 NDPSC Meeting. The Committee considered the November 1996 decision remained appropriate and that clotrimazole for vaginal use should remain in Schedule 3.

The February 2006 NDPSC Meeting considered a new submission from XXXX requesting the rescheduling of clotrimazole for vaginal use to Schedule 2. After due consideration of the new data presented, the Committee agreed that the current scheduling of clotrimazole remained appropriate. Specifically, it was felt that maintaining mandatory pharmacist involvement in the sale of clotrimazole was needed to fully address the Committee's concerns, particularly the risk of repeated clotrimazole use masking an underlying serious condition.

DISCUSSION

A submission was received from XXXX requesting rescheduling from Schedule 3 to Schedule 2 for clotrimazole in vaginal preparations. XXXX submission asserted that:

- The efficacy of clotrimazole had been confirmed in numerous clinical trials which had demonstrated it as an effective treatment for vaginal and vulvovaginal candidiasis. These clinical data are supported by over 25 years of post marketing experience. *In vitro*, clotrimazole kills 99.9% of *Candida albicans* and 95% of *C. glabrata* in 6-18 hours. *In vivo* studies show 70-90% of thrush symptoms resolve within 1-2 weeks of clotrimazole pessary treatment. Maximum relief of symptoms is seen within 3 days. The safety profile for clotrimazole is also well defined and both the pessaries and creams are generally well tolerated after local application. The only adverse effects observed in clinical studies were slight to moderate topical irritation such as burning, reddening and or itching.
- Uncomplicated vaginal candidal infections are easily recognised and treated. The causative agent is yeast, the most common of which (over 80%) is *Candida albicans.* Candida infections are distinctive from other types of vaginal infections in that the discharge can be described as a 'thick cottage cheesy-like' discharge with little or no odour, whereas other vaginal infections such as vulvovaginitis, gardenerella or trichomonas infections are usually malodorous and can be described as watery yellowish or green in colour.
- Three out of four women suffer from a yeast infection at least once in their lives and approximately 40 to 50% will experience a second attack. Approximately 5% have chronic recurrent vulvovaginal candidiasis and in patients experiencing a re-occurrence of a previously diagnosed infection the symptoms and severity are easily recognised by the individual.
- XXXX quoted a paper by Pharmacy Self Care entitled "Issues in women's Health: treatment of vaginal thrush" which asserted that 3 in 4 women are likely to choose a thrush treatment which they have already used in the past (this may reflect their need to be confident about the treatment and familiar with its use). The paper also stated that 88% of women are very unlikely to use a new treatment without seeking advice from the pharmacist or pharmacy assistant.
- With appropriate training, pharmacy assistants can use tools to ensure correct use of the product, including possible continued use if there is any potential for an underlying untreated condition. These training materials consist of a module on vaginal thrush management and a Thrush Recommendation Tree and have been endorsed by the peak pharmacy bodies.
- However, Schedule 2 status does not exclude the patient from obtaining pharmacist advice if required. Indeed, the training tools for pharmacy assistants direct them to refer the patient to the pharmacist in certain circumstances.
- Consumers do read, comprehend and heed the labelling of Pharmacy Only (Schedule 2) products.

- The product labelling has been revised from the previous submission and both the labelling and CMI has been consumer tested by XXXX to ensure that consumers can understand the labelling and would use the product appropriately. This testing showed that consumers were able to find 95% of the information they were looking for and then understand 94% of what they found. They were able to find things easily 87% of the time.
- The labelling highlights that medical advice is recommended before the first course of clotrimazole treatment and this would reduce any risk or potential for undiagnosed underlying conditions. The current proposed labelling and pack insert for clotrimazole, cautions against inappropriate usage and clearly advises that where symptoms do not resolve within 4 days, patients should see a doctor. It also gives further advice prior to use in the following circumstances:
  - For a first infection.
  - In patients under 18 years of age.
  - In patients experiencing 3 or more infections in the last 6 months.
  - In pregnancy (or suspected pregnancy).
  - In patients with diabetes.
- XXXX
- Even in the event of a consumer having undiagnosed diabetes, diabetics would likely present with a number of other symptoms before a vulvovaginal candida infection, thus the potential for clotrimazole use to mask diabetes is not considered to be a major risk. Recurring thrush would not be a primary symptom of undiagnosed or insufficiently treated diabetes. There is also considerable information in the consumer leaflet about thrush and diabetes.

XXXX submission proposed the following wording for the clotrimazole SUSDP entries reflecting XXXX rescheduling request.

Schedule 2

CLOTRIMAZOLE for human use in vaginal preparations and dermal **except** in preparations for the treatment of tinea pedis.

Schedule 3

Delete entry

Schedule 4

CLOTRIMAZOLE **except:**

(a) when included in Schedule 2, 3 or 6; or

(b) in preparations for dermal use for the treatment of tinea pedis.

Schedule 6

CLOTRIMAZOLE for the external treatment of animals

Appendix F Part 3

Poison	**Warning Statements**
Clotrimazole in vaginal preparations when included in Schedule 2	54, 63, 64, 66

NDPSC evaluation report

The NDPSC evaluation report recommended rejection of the proposal to reschedule clotrimazole for vaginal use from S3 to S2. The following points were highlighted in the report:

- The submission had previously been rejected by the NDPSC due to concern regarding a potential lack of pharmacist intervention where a consumer has been using the substance to treat symptoms of recurring thrush which may reflect another serious, underlying condition eg diabetes.
- In the current submission the sponsor claimed that consumers do understand and take note of the labelling on this product and that pharmacy assistants can be trained correctly to use tools to deal with any issues of appropriate use including those relating to underlying medical conditions. However, these tools are not currently validated.
- In the current submission the sponsor provided reports of consumer testing of package labelling and CMIs. The research suggested that the majority of consumers and pharmacy assistants tested understood the labelling statements, although there was some consumer difficulty with understanding the CMI. However there were a number of major limitations to these surveys which make them of limited utility. Namely, there was a very small number of subjects tested XXXX and the design of the study requested the subjects to read the packaging and CMI, which does not reflect the real world experience where this would be a consumer choice.
- The sponsor also stated that even if the consumer had undiagnosed diabetes there would be symptoms other than thrush to suggest this. However, the consumer may

not be aware of symptoms suggesting the onset of diabetes and also not link them with vaginal thrush. Thus, if this product were made S2, there would still be the problem, despite warning labels, of a pharmacist not being available to ask specific questions relating to the onset of this condition.

- Given this, the evaluator remained concerned that S2 availability of clotrimazole would imply, in the consumer's mind, that there was adequate safety of use without direct pharmacist input and advice. However this is not necessarily the case, considering consumers may not adequately read warning labels in this setting and self-identify symptoms of diabetes. Further, the lack of valid pharmacy assistant tools and the small, limited utility surveys presented did not provide any supportive data to currently accept S2 availability of clotrimazole.

XXXX provided a response to the NDPSC evaluators' report in which XXXX contended that Schedule 2 is an appropriate Schedule for clotrimazole for vaginal use. XXXX had also submitted new information, in the form of a study into the treatment of candida vaginitis and vulvitis as part of this response contrary to the guidelines for pre-Meeting responses. XXXX main points were:

- The basis for rejection by the evaluator seemed to be a perceived risk that consumers may not adequately read warning labels and therefore not self-identify symptoms of another serious underlying condition such as diabetes. However, XXXX felt that XXXX had adequately addressed these concerns by using validated research and that these objections were unsubstantiated.
- XXXX noted that the evaluator referred to a pharmacist not being available in a more targeted fashion to ask questions relating to diabetes onset if this substance is given an S2 listing. XXXX stated that pharmacist advice is available if required for Schedule 2 listed substances and also that the training tools developed for pharmacy assistants direct them to refer to pharmacists in certain situations.
- In response to the evaluators' statement that the training tools have not been validated XXXX stated that the training tools for pharmacy assistants had been endorsed by XXXX and are used as part of their self-care program. XXXX also noted that XXXX has requested the use of these materials for training its members.
- XXXX recognised that diabetes is a major and growing concern for all health authorities in Australia; however a study by Dennerstien *(Dennerstein G, "The treatment of Candida vaginitis and vulvitis" Australian Prescriber Vol. 24 No. 3 2001)* showed that the majority of sufferers of recurrent candidiasis are healthy women and the vast majority will not be diabetic. The changes to the labelling of the proposed S2 clotrimazole products would ensure that attention has been drawn to the potential for recurring thrush to be a symptom of another condition and diabetes is specifically mentioned as one of these.
- In response to the evaluators comments about the limitations of the label comprehension testing, XXXX noted that the testing method used is not a survey

style, rather it is a specific type of testing known as 'diagnostic' testing and that cumulative evidence from many studies (many outside the field of health information) shows that the first 6 people participating in diagnostic testing help identify approximately 80% of the faults in a design and after 10 people, no new data on faults comes to light. XXXX also noted that Therapeutic Goods Order 69A refers to a labelling code of practice which states that diagnostic testing is the appropriate method for testing label performance.

- XXXX referred to the NDPSC Meeting 46 Record of Reasons in which the Committee noted that there seemed little risk in deregulation of clotrimazole to S2 as interaction with a pharmacist was unlikely to improve diagnostic accuracy, that if appropriate self diagnosis was made there would be a high cure rate and failure of therapy would be expected to prompt patients to seek medical advice, toxicity and safety of the substance are well established and the Committee accepted that clotrimazole vaginal preparations meet the criteria for a Schedule 2 substance.
- XXXX felt that XXXX had adequately demonstrated through consumer testing that consumers do read and understand the product labelling and this labelling highlights that medical advice is required before the first course of treatment which would reduce the risk or potential for underlying conditions remaining undiagnosed, XXXX maintained that inclusion in Schedule 2 does not mean a lack of pharmacist advice and the tools for pharmacy assistants will ensure that customers are directed to pharmacists if required. XXXX reiterated that recurring thrush would not be a primary symptom of undiagnosed or uncontrolled diabetes and there is information on the labels and in the CMI regarding this issue.

XXXX provided submissions in which XXXX stated that not all vaginal infections are sensitive to clotrimazole, thus XXXX would agree with the proposal provided that the substance was used after an initial medical diagnosis of thrush.

XXXX provided a submission in which XXXX stated that XXXX are opposed to this proposal on the grounds that not all vaginal infections are sensitive to clotrimazole and "self diagnosis" of thrush can lead to a significant risk of misdiagnosis. XXXX believed that the substance should only be available after diagnosis by a medical practitioner or consultation with a pharmacist.

XXXX provided a submission in which XXXX stated that XXXX were opposed to the rescheduling of clotrimazole from Schedule 3 to Schedule 2. XXXX main points were:

- XXXX noted that the Guidelines describe a Schedule 2 substance as one which is used for minor ailments which are easily recognised by the consumer and which do not require medical diagnosis or management. They must also have a low risk of masking a serious disease. XXXX also noted that the Guidelines for Schedule 3 substances require counselling or advice from a pharmacist and are for ailments where the risk of masking a serious condition can be managed by the pharmacist.

- XXXX had concerns regarding the ability of consumers to self diagnose vulvo-vaginal candidiasis (VVC) and the potential for clotrimazole to mask more serious conditions, particularly in patients who are immuno-compromised. XXXX quoted a study *(Ferris, DG, Nyrijesy, P, Sobel JD et al; Over the counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. Obstetrics & Gynecology 2002; 99: 419- 425)* that showed only one third of women who self diagnosed VVC were accurate in their diagnosis and that reading the label did not improve this accuracy. The study also noted that inaccurate self-diagnosis and unsuitable treatment can lead to an unhealthy vaginal ecosystem and may put them at risk of other serious medical conditions. This inability for accurate self-diagnosis should limit the rescheduling of clotrimazole as one of the criteria for Schedule 2 status is that the condition is easily recognisable by the consumer.
- The risk of masking a serious underlying condition is also another criteria that does not meet the guidelines for Schedule 2 status. Recurrent VVC could be symptomatic of conditions such as diabetes, sexually-transmitted disease or immunosuppression.
- XXXX noted that placement of a substance in Schedule 2, in every jurisdiction bar Queensland and Western Australia, means that the consumer can self select the item without the need to consult any staff member at all. Including this substance in Schedule 2 may increase the risk of patients treating more serious conditions without attempting (due to embarrassment) to obtain advice. This in turn would increase the risk of misdiagnosis and unsuccessful/ unsuitable treatment.
- Given the above, XXXX believed the most suitable schedule for clotrimazole was Schedule 3.

A Member noted that the term ‘validated’ in the NDPSC evaluation report was referring to whether the pharmacy assistant training materials had been validated against other standard means of diagnosing patients at a Schedule 2 level. The Member also noted that this may mean that pharmacy assistants may not be asking patients questions directed at diabetes diagnosis when they are discussing clotrimazole use with a patient.

Members discussed the consumer package labelling and CMI testing provided by a sponsor. A Member noted that the major limitation of this testing related to the very small number of subjects tested and that both the patients and pharmacy assistants had been directed to read the labelling and CMI, something which does not happen in the real world. While the testing showed that when read, the CMI and labelling was understood, it did not address the question of whether the documents would be read in the first place.

Members discussed whether labelling and the CMI changes adequately addressed concerns of down-scheduling to Schedule 2, as claimed by the sponsor. The Committee considered whether there was a public health need to down-schedule this substance. A Member stated that if sold within pharmacy environment, there is an opportunity for the labelling to convey most of the information and that there is a pharmacist there if the

patient had any questions, but there is not a need for a pharmacist to intervene in every purchase.

Another Member disagreed with the previous statement that intervention by a pharmacist is not always required, as a woman who has thrush for a third, fourth or fifth time really does need some form of medical intervention as there is most likely to be some form of underlying pathology. Another Member noted that the training material states that a patient presenting for the third time to purchase the substance should be referred to the pharmacist. Another Member stated that it cannot be guaranteed that a patient will go back to the same pharmacy every time to purchase the substance, intervention needs to occur at every purchase to ensure that this possibility will be explored, otherwise the patient may fall under the radar.

A Member noted that each of the jurisdictions are different in their application of the storage of Schedule 2 medicines and in only two of these is there restricted access to Schedule 2 substances. The Member noted that in other jurisdictions it is most likely that, given the embarrassing nature of the condition being treated, that patients will not take up the opportunity to speak to a pharmacist if they have further questions.

OUTCOME

The Committee agreed that the current scheduling of clotrimazole for vaginal use remained appropriate as maintaining mandatory pharmacist involvement in the sale of clotrimazole was needed to fully address the Committee's concerns, particularly the risk clotrimazole being inappropriately used repeatedly without referral to either a pharmacist or doctor or being used incorrectly on non-candidal vaginal infections.

12.1.5 CHLORHEXIDINE

PURPOSE

The Committee considered exempting from scheduling, chlorhexidine in preparations for procedural and surgical hand washes.

BACKGROUND

Chlorhexidine is a chlorophenol biguanide disinfectant with a broad antimicrobial spectrum. Because of chlorhexidine's cationic nature, its mode of action was thought to involve interaction with phosphates on the bacterial cell surface, then disruption of the cytoplasmic membrane with consequent leakage or precipitation of cytoplasmic components.

The May 1974 Poisons Scheduling Committee exempted chlorhexidine from scheduling, but no rationale was given in the minutes.

The August 1995 NDPSC meeting deleted Appendix B, and consequently chlorhexidine, from the SUSDP.

The February 2003 NDPSC meeting reinstated Appendix B to the SUSDP and, consequently, chlorhexidine on the grounds of low toxicity, limited data and the availability of registered or listed products (therapeutic goods).

The October 2005 NDPSC meeting considered the scheduling of chlorhexidine at the request of the Office of Chemical Safety (OCS). As part of the Phase III Review of the FAISD Handbook, the OCS reviewed the first aid instructions and established safety directions for an antiseptic/disinfectant product containing chlorhexidine gluconate that was not covered by existing entries. As a result, it became evident that the eye irritancy properties of chlorhexidine were sufficient to warrant reconsideration of its scheduling.

The October 2005 NDPSC meeting noted:

- the OCS evaluation recommendation of a Schedule 7 entry for chlorhexidine for the treatment of animals with a cut-off to Schedule 5 at 2.5% chlorhexidine (expressed as base) and to unscheduled at 1% or less of chlorhexidine (expressed as base);

- the toxicology concerns outlined in the OCS evaluation report and considered broadening the OCS recommendation from animal use to all uses;

- there are around 40 chlorhexidine products in Australia that are registered for veterinary disinfectants and antiseptics, such as in veterinary surgery, teat dips and sprays, various other topical ointments, creams, sprays, lotions and medicated foams and shampoos, oral rinses and sprays, and in pessaries. Concentrations of chlorhexidine in these products vary from up to 62 g/L chlorhexidine digluconate in concentrated teat dips/sprays to 0.1 g/kg chlorhexidine diacetate in an eye ointment for companion animals; and

- there are around 97 chlorhexidine products in Australia that are registered for human therapeutic use, such as lotions, washes and creams for disinfection and cleaning skin wounds and as oral gels, sprays and mouthwashes for mouth infections;

- there was no Schedule 6 cut-off recommendation in the OCS evaluation and to minimise regulatory impact a 3% exemption to Schedule 5 was considered;

- any scheduling change would have a considerable regulatory impact on both veterinary and human therapeutic use products.

To allow for wider consultation with industry and to encourage submission of information that would support further cut-off levels, the October 2005 NDPSC meeting agreed to foreshadow the inclusion of chlorhexidine in Schedule 7 on the basis of severe eye irritancy. The meeting also agreed that the toxicology data justified an exemption to

Schedule 5 for 3 percent or less and an exemption to unscheduled for 1 percent or less and that there were insufficient data to justify a Schedule 6 exception.

The February 2006 NDPSC meeting considered advice from ADRAC, which included data obtained from a 2005 review of ADRs associated with chlorhexidine. The NDPSC noted that the ADRAC reports were of concern:

- allergic reactions were of most concern for products containing chlorhexidine and it was clear from the available data that these products can very occasionally be associated with severe, even life-threatening adverse events;

- that ADRAC considered that topical chlorhexidine can cause serious topical adverse reactions rarely, and recommended that consumers who use or dispense products containing chlorhexidine should be provided with this information;

- that products such as XXXX contain benzydamide in addition to chlorhexidine, and that benzydamide is also know to cause allergic reactions;

The February 2006 NDPSC meeting further noted that:

- the classification guidelines in respect to eye irritancy for Schedule 6 and Schedule 7 substances suggested that chlorhexidine may be more appropriately included in Schedule 6;

- the lack of actual reports of eye irritancy in actual use suggested that chlorhexidine should be scheduled on the basis of risk rather than hazard. This approach was reinforced by the fact that the main problems seemed to be allergic reactions;

- and that despite widespread use in hospitals and in the dairy industry, there had been no reported problems in use, especially in the dairy industry;

- there be consistency in approach with caustic substances which were included in Schedule 6.

The February 2006 NDPSC meeting agreed, on the basis of the potential for severe eye irritancy, to include chlorhexidine in Schedule 7 of the SUSDP with a cut-off to Schedule 6 for preparations containing 7% or less, Schedule 5 for 3% or less and an exemption to unscheduled for 1% or less when in solid preparations (as solid preparations would not present an eye irritancy hazard to the user).

DISCUSSION

XXXX requested that chlorhexidine in procedural and surgical hand washes be exempted from the labelling and (particularly) container requirements of Schedule 5 of the SUSDP.

XXXX

In XXXX submission, XXXX state that

- XXXX products have a long history (18 years) of safe and effective use by healthcare professionals in the hospital/surgery environment. Only one complaint for skin irritation had been received over the period January 2005 to August 2006 during which time total sales were XXXX;

- XXXX labels already carry the statements *"For external use only"* and *"Keep out of eyes and ears"*. Given the use of the products and the environment in which they are used, the inclusion of the Schedule 5 label signal headings, warning statements and safety directions will not add to the product's safety. The requirement to have *"POISON"*, *"NOT TO BE TAKEN"* either embossed, indelibly written or printed on an irremovable, permanent self adhesive label on the product is particularly onerous. It is incongruous to require a product approved by the TGA as a procedural or surgical handwash to be packaged in a container labelled/embossed *"POISON"*.

- the vast majority of the XXXX products are supplied in the 500 ml and 1.5 L pack sizes mounted on wall brackets for ease of dispensing. Both the 1.5 L bottle and wall bracket are custom made and the product cannot be used without the aid of the wall bracket. It is extremely unlikely that the content of a wall bracket mounted bottle will be spilt and it is out of the reach of children;

XXXX also expressed their dismay that sponsors of products containing chlorhexidine were not notified of the change.

Pre-meeting submission

Pre-meeting submissions supporting the proposal to exempt procedural and surgical handwashes from capture by the Schedule 5 entry, noting use by health care professionals, were received from XXXX

It was noted that at the February 2002 NDPSC Meeting, the Committee had noted that, due to the lack of a Schedule 6 cut-off recommendation in the OCS evaluation (because of a lack of data on toxicology of intermediate strength chlorhexidine), many currently unscheduled human therapeutic products would become Schedule 7 if the OCS recommendations were adopted beyond the treatment of animals (i.e. 4% chlorhexidine gluconate products would be Schedule 5 as they have 2.24% chlorhexidine while 5% chlorhexidine products would be Schedule 7 as they have 2.8% chlorhexidine). The February 2002 NDPSC Meeting therefore considered a 3% exemption to Schedule 5 to minimise regulatory impact.

The February 2007 NDPSC Meeting noted that the OCS had reaffirmed that test findings on 4% chlorhexidine gluconate (ie 2.2% chlorhexidine base) supported the Schedule 5

entry because at this strength, reversible corneal eye injury is produced. The Meeting noted that it was also reaffirmed that preparations containing 4% chlorhexidine gluconate are covered by the existing Schedule 5 entry (ie 3% or less chlorhexidine). The SUSDP entry is expressed as a percentage of chlorhexidine base, not salt.

On this basis, XXXX products XXXX are appropriate for inclusion in Schedule 5 and require only the Signal Heading of CAUTION and not POISON as suggested. Data was available to the OCS demonstrating corneal de-epithelialisation and increased corneal thickness associated with concentrations of 4% chlorhexidine gluconate.

OUTCOME

The Committee agreed that the current scheduling of chlorhexidine remained appropriate.

12.2 SUSDP, PART 5

12.2.1 HYDROQUINONE

The Committee considered a request from XXXX to amend the Appendix E entry for hydroquinone.

BACKGROUND

Hydroquinone is a reducing agent and it oxidizes to form quinone in air. It is used as a photographic developer, antioxidant, stabilizer in paints, fuels, oils, and polymers, as a chemical intermediate, in pharmaceuticals, and as a skin depigmenting agent. Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. It is used topically as a depigmenting agent for the skin in hyperpigmentation conditions such as chloasma (melasma), freckles, and lentigines (small macules that resemble freckles). Concentrations of 2 to 4% are commonly used; higher concentrations may be very irritant and increase the risk of ochronosis.

XXXX requested that the Appendix E entry for hydroquinone be amended to reflect that Schedule 2 hydroquinone products (ie, preparations containing <2% for human external therapeutic or cosmetic use) requires only standard statement A. XXXX advised the Committee that standard statements G2, G3, S1, E2 and R2 were inappropriate for Schedule 2 hydroquinone products as there was no corresponding “skin” warning under the old pre-2004 statements and it was extremely unlikely that anyone could swallow or get in the eyes enough of a 2% cream to cause serious adverse effects.

DISCUSSION

The Committee noted pre-Meeting comment from XXXX expressing interest in the consideration of hydroquinone and reserving the right to make comment on the outcome of consideration.

The Committee was informed that bleaching products were not deemed to be safe by the FDA and that they were under review in the USA because of concerns about carcinogenicity with regard to topical use and blue-black skin discolouration with lower concentrations.

DECISION 2007/49 - 24

The Committee agreed to amend the Appendix E entry for hydroquinone to reflect that Schedule 2 hydroquinone products require only standard statement A. The Committee also agreed that the US review be monitored for future consideration of the Committee.

APPENDIX E, Part 2 – Amendment

Hydroquinone – Amend entry to ready:

Hydroquinone

- when included in Schedule 2 A
- when included in Schedule 4 and 6 A,G2,G3,S1,E2,R2

13. MATTERS REFERRED BY AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC)

13.1 NEW SUBSTANDES (NOT SEEN BEFORE BY NDPSC)

13.1.1 NATALIZUMAB

PURPOSE

The Committee considered the scheduling of a new medicine, natalizumab.

BACKGROUND

Natalizumab is an alpha-4 integrin-specific humanised monoclonal antibody.

The August 2006 (247th) ADEC meeting found that there was sufficient evidence of safety and efficacy to recommend:

- that there should be no objection to approval of an application from XXXX containing the new medicine natalizumab for the indication:
  as monotherapy for the treatment of patients with relapsing and remitting multiple sclerosis [RRMS] *to delay the progression of physical disability and to reduce the frequency of relapse. The safety and efficacy of* XXXX *beyond two years are unknown;*

- approval is subject to finalisation of the Product Information to the satisfaction of the TGA;
    - XXXX

DISCUSSION

The meeting noted the following Black Box Warning as recorded in Micromedex Drugdex for natalizumab:

Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with natalizumab monotherapy.

- *Because of the risk of PML, natalizumab is available only through a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, natalizumab must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program.*

- *Healthcare professionals should monitor patients on natalizumab for any new sign or symptoms that may be suggestive of PML. Natalizumab dosing should be withheld immediately at the first sign or symptoms suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.*

The Committee also noted that the XXXX PI states that XXXX therapy is to be initiated and supervised by neurologists, in centres with timely access to MRI.

DECISION 2007/49 - 25

The Committee agreed to include natalizumab in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine requires patient management, monitoring and administration by a medical professional

Schedule 4 – New entry

NATALIZUMAB.

13.1.2 GADOFOSVESET TRISODIUM

PURPOSE

The Committee considered the scheduling of the new chemical gadofosveset trisodium.

BACKGROUND

Gadofosveset is a gadolinium chelate used as a paramagnetic contrast medium (Contrast Media) in magnetic resonance angiography. It binds to plasma proteins, particularly albumin, and therefore acts as a blood pool agent, allowing visualisation of the vasculature.

The August 2006 (247th) ADEC meeting found that there was sufficient evidence of safety and efficacy to recommend that:

- there should be no objection to approval of the submission from XXXX to register XXXX containing the new chemical gadofosveset XXXX for the indication:
  for contrast-enhanced magnetic resonance angiography for visualisation of abdominal or limb vessesls in patients with suspected or known vascular disease;

- approval should be subject to finalisation of the Product Information to the satisfaction of the TGA.

DISCUSSION

In XXXX pre-Meeting submission, XXXX requested that gadofosveset be considered for exemption under the Appendix A entry for 'Radiographic Contrast Media'. XXXX stated that this would be consistent with the scheduling of other gadolinium-containing MRI agents such as gadobutrol and disodium gadoxetate as these products are supplied directly to radiology departments and administered by trained personnel.

The November 1999 NDPSC Meeting considered the rescheduling of radiographic contrast media for use by injection from Appendix A to Schedule 4 as part of trans-Tasman harmonisation. That meeting agreed that *on the basis of radiographic contrast media being diagnostic agents with no other therapeutic use, their use under direct medical supervision and the lack of availability to the general public, the media should not be included in Schedule 4.*

The Committee noted that the US FDA released a safety advisory on 8 June 2006 about gadolinium-containing contrast agents and a disease known as Nephrogenic Systemic

Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD) that occurs in patients with kidney failure.

The Committee noted the FDA Public Health Advisory Statement of 22 December 2006 which reported that:

- NSF/NFD may occur in patients with moderate to end-stage kidney disease after they have had a Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA) scan with a gadolinium-based contrast agent;

- as at 21 December 2006, the FDA received reports of 90 patients with moderate to end-stage kidney disease who developed NSF/NFD after they had an MRI or MRA with a gadolinium-based contrast agent;

- NSF/NFD began from 2 days to 18 months after exposure to the contrast agent;

- many, but not all of these patients, received a high dose of the contrast agent; some received only one dose;

- FDA was notifying health care providers and patients of the AE, the symptoms to watch for, remedial action to be taken and the reporting requirements;

- worldwide, about 215 patients with NSF/NFD have been reported; the medical histories of 75 of these patients have been reviewed in detail; all of the patients had received a gadolinium-based contrast agent for an MRI or MRA; researchers have identified gadolinium in skin biopsies of patients with NSF/NFD;

- the FDA was working with expert scientists to gather additional information about NSF/NFD and to find out why it occurs in patients with moderate to end-stage kidney disease who receive gadolinium-based contrast agent;

- currently there are five FDA approved gadolinium-based contrast agents XXXX for use during an MRI scan, but not for use during an MRA scan. Although NSF/NFD has been reported for only 3 of the 5 gadolinium-based contrast agents, FDA believes that there is a potential for NSF/NFD to occur with the use of any of the approved gadolinium-based contrast agents.

The FDA had also published a Q & A document on this issue on their website.

XXXX has advised that:

- XXXX had not specifically considered gadolinium-based contrast agents in the past and XXXX had been included in the XXXX agenda;

- XXXX had received relatively few reports for paramagnetic contrast agents (essentially gadolinium based agents) with no reports of renal problems being received in this context and most reports describing the usual range of hypersensitivity reactions, rashes, bronchospasm, etc. as seen with other contrast agents.

The February 2007 NDPSC Meeting acknowledged that the link had not been definitely established and agreed that the consideration by USFDA, XXXX and XXXX be monitored with updates to be provided to the Committee.

OUTCOME

The Committee agreed that gadofosveset should fall under the general Appendix A scheduling exemption of "radiographic contrast media (radiopaques) for therapeutic use" on the grounds that this is consistent with the scheduling of other radiographic contrast media and that the product is supplied directly to hospital radiology departments and only administered by trained personnel.

13.1.3 IVABRADINE

The Committee considered the scheduling of the new medicine, ivabradine.

BACKGROUND

The August 2006 (247th) ADEC meeting found that there was sufficient evidence of safety and efficacy to recommend that:

- there should be no objection to the approval of the submission from XXXX to register XXXX tablets containing the new chemical ivabradine XXXX for indications:

  treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are unable to tolerate or who have a contraindication to the use of beta blockers;

- approval should be subject to finalisation of the Product Information (PI) to the satisfaction of the TGA.

DISCUSSION

The Meeting noted that ivabradine is classified as a Pregnancy Category D medicine in the Australian PI XXXX and that the *Use in Pregnancy* precaution in the PI records that *animal reproduction studies have shown embryotoxic and teratogenic effects (cardiac defects in rats and ectrodactylia) at exposures (based on AUC) close to the clinical exposure at 7.5 mg b.i.d. There are no adequate data concerning the use of ivabradine in pregnant women. Ivabradine is contraindicated during pregnancy as the potential risk*

for humans is unknown. The Committee also noted that Micromedex Martindale only reports that *studies in animals have shown that ivabradine is embryotoxic and teratogenic and is distributed into breast milk.*

The Committee noted that Pregnancy Category D is positive evidence of human foetal risk exists, but benefits in certain situations may make use of the drug acceptable despite its risks. The Committee also noted that XXXX

The Committee agreed that, as there is no human data on human foetal risk and that the PI specifically contraindicates pregnancy, listing in Appendix D was not warranted.

DECISION 2007/49 - 26

The Committee agreed that ivabradine be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitate appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional. The inclusion of ivabradine in Schedule 4 harmonises the scheduling of this substance with New Zealand.

Schedule 4 - New entry

IVABRADINE.

13.1.4 SUNITINIB

PURPOSE

The Committee considered the scheduling of the new medicine, sunitinib (as malate).

BACKGROUND

Sunitinib (as malate) is a multi-targeting receptor tyrosine kinase inhibitor, decreasing tumor cell proliferation and angiongenesis.

The August 2006 (247th) ADEC meeting found that there was sufficient evidence of safety and efficacy to recommend that:

- there should be no objection to the approval of the submission from XXXX to register XXXX capsules containing the new chemical entity sunitinib XXXX for the indications:
    - *the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance;*
    - *the treatment of advanced renal cell carcinoma (RCC);*

- XXXX;

- approval should be subject to finalisation of the Product Information to the satisfaction of the TGA.

DISCUSSION

XXXX

The XXXX (sunitinib) PI also recorded that:

- carcinogenicity studies had not been performed;

- no studies on the effects on the ability to drive or operate machinery had been performed and patients should be advised that they may experience fatigue or dizziness during treatment with XXXX.

XXXX

Sunitinib has been classified as a Pregnancy Category D medicine in the Australian PI XXXX The *Use in Pregnancy* precaution in the PI records that *there are no studies in pregnant women using sunitinib …* XXXX *should not be used during pregnancy. Women of childbearing potential must be advised to avoid becoming pregnant while receiving treatment with* XXXX *… adequate contraception should be used during therapy and for at least 4 weeks after completion of therapy.*

Micromedex Drugdex recorded sunitinib as a Pregnancy Category D and stated that *there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.)* Drugdex further states that *no human studies of pregnancy outcomes after exposure to sunitinib have been published and there have been no reports of outcomes after inadvertent exposure during pregnancy.*

The Committee noted that Pregnancy Category D is positive evidence of human foetal risk exists, but benefits in certain situations may make use of the drug acceptable despite its risks. The Committee also noted that XXXX

The Meeting agreed that as there had been no studies in pregnant women or no human studies of pregnancy outcomes have been published or no reports of outcomes after inadvertent exposure during pregnancy and that the PI specifically contraindicated pregnancy, listing in Appendix D was not warranted.

DECISION 2007/49 - 27

The Committee agreed that sunitinib be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitates appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional. The inclusion of sunitinib in Schedule 4 harmonises the scheduling of this substance with New Zealand.

Schedule 4 – New entry

SUNITINIB.

14. OTHER MATTERS FOR CONSIDERATION

14.1 CHILD RESISTANT PACKAGING

PURPOSE

The Committee noted the current position regarding Standards Australia's review of the child-resistant packaging standard/s.

BACKGROUND

The October 2006 NDPSC Meeting noted:

- the South Australian Coroner's report into the death of a child from morphine toxicity after gaining access to medication contained in blister packaging;
- the Coroner's recommendation that the Minister for Health give consideration to the introduction of appropriate standards in South Australia for the child-proofing of blister packaging for hazardous pharmaceuticals;
- correspondence of July 2006 from the SA Minister for Health to the Australian Minister for Health requesting *"that you identify a way to progressively improve the safety of blister packs used in Australia, in particular for the most hazardous medications, as per overseas practice";*
- a response from the Australian Minister for Health to the SA Minister for Health advising that the matter would be referred to the Therapeutic Goods Committee (TGC) and the National Drugs and Poisons Schedule Committee (NDPSC);
- the TGC recommended that the Australia New Zealand Therapeutic Products Authority (ANZTPA) initiate a process of consultation and liaison with the pharmaceutical industry in order to develop practical and effective requirements for non-reclosable packaging that will assist in further reducing the potential for accidental childhood poisoning from medicines packaged in this way;

- Standards Australia were looking at reviewing Australia's CRP standards.

The October 2006 NDPSC Meeting agreed that XXXX CRP issues were being progressed by XXXX Standards Australia, the Committee XXXX would monitor progress for the information of future NDPSC meetings.

DISCUSSION

In April 2006, Standards Australia approved a project to review the current standard and requirements for child-resistant packages, namely AS 1928:2001. The basis of the project was a request from a Queensland Injury Surveillance Unit and follows a review of regulatory requirements for child-resistant packaging of medicines.

The review is being undertaken by the Standards Australia Packaging Systems and Devices – Child Resistant Chemicals Committee (PSD-CRC). The project has been given a public comment target of 6 April 2007 and a final approval target of 3 December 2007.

The prime function of the review is the standardisation in the field of child-resistant packaging systems and devices and to monitor and participate in similar work being undertaken by ISO/TC 122 Packaging, with participation in the work of international technical committees, subcommittees and working groups including ISO/TC 122 / SC 3 / WG 3: Child Resistant Containers.

> Technical Committee *TC 122 – Packaging* (scope: Standardization in the field of packaging with regard to terminology and definitions, packaging dimensions, performance requirements and tests.)
>
> > Sub-Committee *SC 3 – Performance requirements and tests for means of packaging, packages and unit loads*
> >
> > > Working Group *WG 3 – Child resistant containers*
>
> International Standard *ISO 8317:2003 Child resistant packaging – Requirements and testing procedures for reclosable packages* falls within the direct responsibility of TC 122 / SC 3.

The proposed constitution of the PSD-CRC Committee as listed on the Standards Australia website is as follows:

Agency	*Known representative*
ACCORD Australasia	XX
Australian Chamber of Commerce & Industry	XX
Australian Institute of Packaging	XX
Australian Self Medication Industry	XX
Commonwealth Department of Health &	XXXX

Ageing	
Consumers' Federation of Australia	XX
Consumers' Health Forum of Australia	XX
Department of Health & Human Services Tasmania	XXXX
Department of Health Western Australia	XX
Department of Human Services (Victoria)	XXXX
National Injury Prevention Advisory Council Standards Working Group	XX
NSW Health Department	XX
Packaging Council of Australia	XX
Pharmaceutical Society of Australia	XX
Plastics & Chemicals Industries Association Incorporated	XX
Royal Children's Hospital, Melbourne	XX
The Children's Hospital at Westmead	XX

At its first meeting in May 2006, the PSD-CRC Committee agreed unanimously to review the current Standard AS 1928 Child-resistant packages.

At its second meeting in October 2006, there was in-principle agreement that the International Standard ISO 8317:2003 should be adopted for the testing of child-resistant reclosable packagings, with appendices that set out Australian variations, in particular the use of reduced test panels and the torque test. For non-reclosable packaging, the PSD-CRC Committee agreed that further work was necessary.

At its third meeting in November 2006, the PSD-CRC Committee agreed to adopt International Standard ISO 8317:2003 and its 2005 technical corrigendum, with an appendix listing Australian variations. The adoption of British Standard BS 8404:2001 for non-reclosable packages was discussed, but there was general agreement that its adoption was inappropriate at present. The PSD-CRC Committee also agreed that a forum on child-resistant packages be held in Sydney in February/March 2007.

A Daily Telegraph news item of 26 September 2006 reported that Standards Australia had confirmed they were looking to review the safety standard for CRPs. The news item also reported that the findings of a study exploring why CRCs fail was to be presented that day at the UNSW National Injury Prevention Conference.

The Daily Telegraph reported on 26 September 2006 that:

- the findings of a study exploring why CRCs fail was to be presented that day at the UNSW National Injury Prevention Conference. Professor Joan Ozanne-Smith, the author of the report, said the research investigated 139 cases of poisong and found in

9 per cent of cases the child opened the case with their teeth and 63 per cent of the containers did not re-engage again properly when resealed;

- Sydney Children's Hospital said about 70 per cent of poison cases presenting to hospital were children under the age four and that the most common poisons were household medications like paracetamol as well as adult medication such as cardiac treatment, sedatives, sleeping tablets and iron tablet were also of concern;

- Standards Australia had confirmed on 25 September 2006 that they were looking to review the safety standard for CRPs.

The Meeting was informed that a forum of interested parties was to be held in Sydney on Friday 23 February 2007 and that the Commonwealth government representative from the TGA is active with the PSD-CRC Committee on this matter.

The Meeting was also informed that XXXX would be attending the forum representing NSW Health and Queensland Health respectively.

OUTCOME

The Committee noted the action being taken by Standards Australia in reviewing the standard/s and requirements for child-resistant packages and agreed that progress be monitored for reporting to future NDPSC meetings.

14.2 UNSCHEDULED ANALGESIC & NICOTINE PRODUCTS – "KEEP OUT OF REACH OF CHILDREN" LABEL STATEMENT

PURPOSE

The Committee considered correspondence from the XXXX concerning "KEEP OUT OF REACH OF CHILDREN" warning statements on unscheduled analgesic and nicotine products.

BACKGROUND

Following investigation of a complaint that a major supermarket chain had been storing unscheduled paracetamol packs in dual level "dump bins", the XXXX informed the Committee that:

- small packs of paracetamol, aspirin and ibuprofen do not carry the cautionary statement "KEEP OUT OF REACH OF CHILDREN";

- the lower level of the storage bin in question was no more than half a metre in height and therefore readily accessible to children;

- the supermarket in question had a policy of storing poisons on shelving above 1.2 metres, however senior management rejected any change regarding the current storage in 'dump bins';

- these medicines are harmful if consumed inappropriately by children;

- the "KEEP OUT OF REACH OF CHILDREN" statement should appear prominently on all packs as it is a warning intended for the attention of both the suppliers of these medicines and the persons storing them in their homes;

- unscheduled medicines are outside the control of the State's Poisons Act and Regulations in respect of specifications such as restricted storage;

DHHS reported that a similar concern existed with unscheduled nicotine replacement products as the toxicity of this compound is well known.

DHHS requested that the Committee make a recommendation to the TGA Over-the-Counter Medicines Section for the inclusion of a requirement for a label statement of "*KEEP OUT OF REACH OF CHILDREN*" in the Required Advisory Statements for Medicines Labels (RASML) with regard to unscheduled paracetamol, aspirin, ibuprofen and nicotine medicines. DHHS also recommended that the warning should be prominent, appearing at the top of the main label and consistent with the requirement for the cautionary statement on a scheduled medicine

OUTCOME

The Committee agreed to recommend to the TGA Over-the-Counter Medicines Section for the inclusion in RASML of a requirement for a label statement of "*keep out of reach of children*" on unscheduled paracetamol, aspirin, ibuprofen and nicotine medicines and that the label statement be prominent, appearing at the top of the main label and consistent with the requirement for the cautionary statement on a scheduled medicine. These substances were of priority concern due to their potential toxicity in accidental ingestion and their correct storage in the home.

While it was agreed that it may not be required with every product, the Committee also agreed to recommend to the TGA that consideration be given for the inclusion in RASML for the label statement "*keep out of reach of children"* to be included on all medicines approved by or listed with the TGA.

XXXX

15. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

Nil items considered.,

16. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

16.1 MCC NEW S4 MEDICINES

PURPOSE

The Committee considered the inclusion in Schedule 4 (S4) of new medicines classified as Prescription Medicines in New Zealand.

BACKGROUND

The 34th and 35th MCC meetings, held in June 2006 agreed to classify the new medicines below, i.e. adrafanil, exenatide, sitafliptin, sorafenib, telbivudine and varenicline as Prescription Medicines and the October 2006 NDPSC meeting agreed to foreshadow their inclusion in S4 to harmonise with New Zealand. The following information was considered by MCC.

Adrafinil

- Adrafinil is a central stimulant and alpha(1)-adrenergic agonist chemically related to modafinil. It is usually used to treat mental function impairment in the elderly. Off-label use by individuals wishing to avoid fatigue has been reported.
- Adrafinil is a prodrug; it is primarily metabolized *in vivo* to modafinil, resulting in nearly identical pharmacologic effects. Unlike modafinil, however, it takes time for the metabolite to accumulate to active levels in the bloodstream.
- The 34th MCC Meeting noted that adrafinil was a potential drug of abuse which was referred to the MCC by the Medsafe Medicines Control Team for classification.

Exenatide

The 35th MCC Meeting noted that:

- Exenatide is an incretin mimetic agent that enhances glucose dependent insulin excretion and mimics several other antihyperglycemic actions of the incretin glucagon-like-peptide1 (GLP-1).
- Exenatide can improve glycaemic control in patients with type 2 diabetes by lowering fasting and postprandial glucose concentrations.
- The proposed indication is as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

Members also noted the following Adverse Effects and Precautions from the Micromedex monograph for exenatide:

- Hypoglycaemia can occur in patients given exenatide, particularly when given with a sulfonylurea. Exenatide commonly causes mild to moderate nausea, which is dose-dependent and tends to decrease with continued therapy in most patients. Other adverse effects include vomiting, diarrhoea, nervousness, dizziness, headache, and dyspepsia. Less frequent reports include asthenia, decreased appetite, gastro-oesophageal reflux, and hyperhidrosis.
- Exenatide should not be used in type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Exenatide clearance is reduced in patients with severe renal impairment and adverse gastrointestinal effects have been reported in these patients.

Varenicline

The 35th MCC Meeting noted that:

- Varenicline is a highly selective partial agonist of the $\alpha 4\beta 2$ acetylcholine nicotinic receptor that was specifically designed for use in smoking cessation. Mainly found in the brain, this receptor mediates the reinforcing properties of nicotine in animal models.
- Because of its agonist properties, varenicline is expected to reduce the severity of nicotine craving and nicotine withdrawal symptoms experienced upon cessation of smoking.
- Additionally, because of its antagonist properties, varenicline is expected to reduce the satisfaction associated with smoking, thereby decreasing the likelihood that a lapse during a quit attempt will lead to a return to regular smoking. These two properties are expected to provide increased rates of abstinence, both at the end of the treatment and in the long term.
- The proposed indication is for smoking cessation.

Sitagliptin

The 35th MCC Meeting noted that:

- Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes.
- The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin phosphate increases the levels of two known active incretin hormones, glucagons-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP).
- Incretin hormones physiologically regulate blood glucose levels by increasing insulin response from pancreatic beta cells and suppressing glucagon secretion from

pancreatic alpha cells when blood glucose levels are normal or elevated. These effects are not observed when blood glucose levels are low.

- Sitagliptin phosphate differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferators-activated receptor gamma PPARγ agonists, alpha-glucosidase inhibitors, and amylin analogues.
- Sitagliptin phosphate is indicated:
  - as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.
  - in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a PPARγ agonist when diet and exercise, plus the single agent, do not provide adequate glycaemic control.

Telbivudine

The 35th MCC Meeting noted that:

- Telbivudine is a specific and selective nucleoside with preferential inhibition of the synthesis of the 2nd strand HBV DNA synthesis.
- Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is efficiently phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours.
- Telbivudine-5'-phosphate inhibits HBV DNA polymerase by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine-5'-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication.
- The proposed indication is the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation.

Sorafenib

The 35th MCC Meeting noted that:

- Sorafenib is a multikinase inhibitor targeting both tumour cells and the tumour vasculature. Sorafenib inhibits tumour growth of the murine renal cell carcinoma, RENCA, and a broad spectrum of human tumour xenografts in athymic mice accompanied by a reduction of tumour angiogenesis.
- The proposed indication is the treatment of patients with advanced renal cell carcinoma.

Members also noted the following from the Micromedex Monograph for sorafenib:

- Safety and effectiveness not established in children.

- FDA labelled indications - Renal cell carcinoma, Advanced.
- Common adverse effects include Hypertension (17%), alopecia (27%), dry skin (11%), hand-foot syndrome due to cytotoxic therapy (30%), pruritus (19%), rash (40%), hypophosphatemia (45%), weight loss (10%), abdominal pain (11%), constipation (15%), diarrhoea (43%), increased amylase level (30%), increased lipase level (41%), loss of appetite, nausea (23%), vomiting (16%), anaemia (44%), lymphocytopenia (23%), neutropenia (18%), thrombocytopenia (12%), arthralgia (10%), myalgia (1% to less than 10%), headache (10%), sensory neuropathy (13%), depression (1% to less than 10%) and fatigue (37%).
- Serious adverse effects include Heart failure (infrequent), hypertensive crisis (0.1% to less than 1%), Ischemic heart disease, acute (0.1% to less than 1%), myocardial infarction (0.1% to less than 1%), erythema multiforme (0.1% to less than 1%), haemorrhage - all body sites (15%), thromboembolic disorder (Infrequent) and acute renal failure (infrequent).
- Sorafenib is classified as Pregnancy Category D. Precautions include a pregnancy teratogenicity risk. Infant risk from breast feeding could not be ruled out.

Members recalled discussion from the October 2005 NDPSC Meeting which discussed the requirements for Appendix K listing of substances. At this Meeting the Committee considered a submission from the XXXX which advised that XXXX quoted a cut-off of 10% incidence of drowsiness for their selection criteria for sedation warnings. The Committee considered that this cut-off (drowsiness or sedation greater than 10% above placebo) could possibly represent a starting point for developing a set of inclusion criteria for Appendix K.

DISCUSSION

A member noted that adrafanil is a pro-drug for modafanil and is being sold on the internet as a stimulant agent. In New Zealand there is no provision for the automatic scheduling of derivatives, so adrafanil was included as a separate entry in the schedules. A member noted that modafanil was a prescription medicine in both Australia and New Zealand and that there was currently no evidence of abuse of either substance. The member noted that if such abuse were to become apparent, then rescheduling could be considered.

The members also noted that the MCC felt that as all of these medications are new medications and that the conditions being treated required medical management, that they should be scheduled as prescription only.

Members discussed the proposed Appendix K listing for sorafenib. The Secretariat noted that it was included as one of the adverse events listed was for fatigue. The Committee discussed this and noted that fatigue does not constitute drowsiness or sedation, thus sorafenib should not be included in Appendix K of the SUSDP.

DECISION 2007/49 - 28

The Committee agreed to include all substances in Schedule 4 of the SUSDP on the basis that appropriate use requires medical diagnosis and management and to harmonise scheduling with New Zealand.

Schedule 4 – New entries

ADRAFINIL.

EXENATIDE.

SITAGLIPTIN.

SORAFENIB.

TELBIVUDINE.

VARENICLINE.

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC)

17.1 [ITEM DELETED]

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

Nil items considered.

19. GAZETTAL NOTICES

The Committee noted the post-October 2006 Gazette Notice No.47 of 29 November 2006

The Committee noted the pre-February 2007 Gazette Notice No.50 of 20 December 2006

20. AMENDMENTS TO THE SUSDP

20.1 EDITORIAL CHANGES AND ERRATA (BECLOMETHASONE, BUDESONIDE, CARBON DISULPHIDE, 2,4-DICHLORPROP, FLUTICASONE, HYDROGEN SULPHIDE, IBUPROFEN, PROCHLORPERAZINE AND TRIAMCINOLONE)

PURPOSE

1. The Committee considered editorial changes and errata.

DISCUSSION

A Member suggested an editorial clarification for the Schedule 2 entries for beclomethasone, budesonide and fluticasone. The clarification would be to add “of age” after “12 years” for consistency with other entries.

The Member also suggested an editorial amendment to the Schedule 3 ibuprofen entry (introduced in SUSDP 21 Amendment 1). For consistency with other entries there should be a comma after "age" at the end of part (b), to clarify that "except when included in or expressly excluded from Schedule 2" applied to the whole entry, not just part (b).

Members also recalled that under item 1.8.1.3.2 a search of the SUSDP noted that sulphide was used 3 times (cadmium sulphide, carbon disulphide, hydrogen sulphide) and that the alternative spelling, sulfide, was also used 3 times (selenium sulfide, potassium sulfide, sodium sulfide). It was noted that sulfide was traditionally spelled "sulphide" in British English, but IUPAC had adopted the spelling "sulfide", as had the Royal Society of Chemistry Nomenclature Committee. Item 1.8.1.3.2 therefore proposed amending the spelling of cadmium sulphide to cadmium sulfide. Members agreed to editorially amending the carbon disulphide and hydrogen sulphide entries for consistency.

Additionally, in the DAP comments received with regard to item 1.8.1.4 a number of minor editorials were identified. These included:

- A hyphen was missing from the 2,4-dichlorprop Schedule 6 entry. Additionally, it was suggested that the “includes the R and S enantiomers” should instead read as “including the R and S enantiomers”. Members agreed to varying decision 2006/48-8 to include these changes.
- An assertion that the Schedule 3 amendment for prochlorperazine should read "in divided preparations for oral use in a primary pack containing ...". Members instead confirmed the October 2006 wording, noting:
    - That the New Zealand classification for prochlorperazine specified “packs”, not “primary packs”.

- That historically "primary pack" had been unharmonised between the SUSDP, TGA and New Zealand definitions. Members agreed to ask XXXX to clarify whether this had been resolved and, if so, what interpretation of "primary pack" will be used. If it had not been resolved, the Committee agreed to recommend to XXXX that this was an issue that needed to be retained on their agenda.

The Secretariat advised of an errata regarding inclusion of triamcinolone in Appendix H. The February and June 2004 NDPSC Meetings decided to rescheduled intranasal preparations for short term use with certain restrictions containing triamcinolone from Schedule 3 to Schedule 2. This decision meant that triamcinolone was only captured in Schedule 3 for the treatment of mouth ulcers (with strength and pack size limits). All other uses of triamcinolone reverted to the Schedule 4 parent entry. However, in making this decision, the Committee inadvertently omitted deletion of the existing Appendix H entry for triamcinolone acetonide in aqueous nasal sprays.

Members also noted that a proposed editorial amendment to the Schedule 4 protirelin entry was discussed and agreed to under Item 1.8.1.5.

DECISION 2007/49 - 29
The Committee agreed to the following editorial changes or errata for inclusion in SUSDP 21 Amendment 3:

- For clarity and consistency, to amend the Schedule 2 entries for beclomethasone, budesonide and fluticasone by adding "of age" after "12 years".
- To amend the Schedule 3 ibuprofen entry to include a comma after "age" at the end of part (b) to clarify that "**except** when included in or expressly excluded from Schedule 2" applies to the whole entry, not just part (b).
- To replace "carbon disulphide" and "hydrogen sulphide" with "carbon disulfide" and "hydrogen sulfide" respectively, for consistency.
- To delete "triamcinolone acetonide in aqueous nasal sprays" from Appendix H as this was inadvertently overlooked by the June 2004 NDPSC Meeting when it decided to reschedule triamcinolone for nasal use from Schedule 3 to Schedule 2.

The Committee also agreed to the following regarding October 2006 NDPSC Decisions:

- To vary decision 2006/48-8 regarding the Schedule 6 2,4-dichlorprop entry by inserting a hyphen after 2,4 and to replace "includes" with "including".
- To confirm decision 2006/48-17 regarding the Schedule 3 prochlorperazine entry.

AMENDMENTS FOR INCLUSION IN SUSDP 21 AMENDMENT 3

Schedule 2 - Amendments

BECLOMETHASONE in aqueous nasal sprays delivering 50 micrograms or less of beclomethasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

BUDESONIDE in aqueous nasal sprays delivering 50 micrograms or less of budesonide per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

FLUTICASONE in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Schedule 3 – Amendment

IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen, in a primary pack containing not more than 50 dosage units when labelled:

(a) with a recommended daily dose of 1200 mg or less of ibuprofen; and

(b) not for the treatment of children under 12 years of age,

except when included in or expressly excluded from Schedule 2.

Schedule 6 – Amendment

CARBON DISULFIDE.

Schedule 7 – Amendment

HYDROGEN SULFIDE.

Appendix E – Part 2 – Amendment

POISON **STANDARD STATEMENT**

Carbon disulfide.....A,G3,E2,R1,S2

Appendix H – Amendment

Triamcinolone acetonide – delete entry.

VARIATION TO OCTOBER 2006 DECISION

Schedule 6 – Amendment (Variation of Decision 2006/48-8)