Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

46th Meeting
21-23 February 2006

TABLE OF CONTENTS

GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
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
ASCC	Australian Safety and Compensation Council
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	*see ASCC*
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

1.7

[Items deleted**]**

1.8 NDPSC WORKING PARTIES

1.8.1

[Item deleted**]**

1.8.1.2 SUBSTANCES IDENTIFIED IN THE OZNZ SCHEDULING DATABASE AS UNHARMONISED

PURPOSE

The Committee considered the foreshadowed decisions from the October 2005 NDPSC meeting based on the recommendations of the TTHWP Meeting 14 (October 2005). The scheduling of the substances below was identified as unharmonised with New Zealand in the OZNZ Scheduling database.

1.8.1.2.1 ACONITUM SPP

BACKGROUND

The October 2005 NDPSC meeting considered a recommendation from MCC to harmonise with New Zealand. In Australia, *Aconitum* spp was in Schedule 4 (S4) while in New Zealand, the primary entry was in Part I (S4) and certain oral and dermal preparations were classified General Sale and Pharmacy Only medicines. The June 2005 MCC minutes indicated that MCC recently classified *Aconitum* spp to allow continued access to complementary products already on the market. Following the October 2005 NDPSC meeting, OCM was asked to comment on the proposal to harmonise the scheduling of *Aconitum* spp with New Zealand.

The MCC Secretary provided a copy of the assessment report on XXXXXXXX proposal to reschedule *Aconitum* spp and to revise the cut-offs specified in the Schedules such that they were expressed in terms of the total alkaloid content rather than the amount of plant material in the preparations. There were no products registered on New Zealand's SMARTI database but there were numerous products listed on the ARTG containing *Aconitum* spp. However, according to the assessment report, the only aconite-containing product(s) being sold as General Sale medicines in New Zealand were homoeopathic liquids or powders containing Aconite 4X (i.e. a 0.01% tincture) for internal administration, which contained a maximum of 0.000015% alkaloids, equivalent to 0.15 micrograms per 1ml (15 drop) dose. The cut-offs adopted in New Zealand were based on pack sizes of such products, i.e. 30ml or 100ml being available, which contained a maximum total amount of 4.5 micrograms or 15 micrograms (0.015mg) alkaloids in each

pack size respectively. MCC noted this was less than 1% of the lowest reported fatal **adult** dose of 2mg.

DISCUSSION

Members noted the pre-meeting submission received from XXXXXXXX reserving the right to make any additional comments following advice of the outcome of the February 2006 meeting and before a decision was finalised.

The Committee noted the advice from OCM which stated the following:

- The OCM agreed with the principle of the MCC proposed scheduling for *Aconitum* species being based on the total alkaloids (the known toxic component) contained in the preparation.
- The OCM was initially concerned that the proposed limit of 0.02 % for the total alkaloids was too high, as severe poisoning had been reported after ingestion of as little as 0.2 mg of the toxic alkaloid aconitine [Tai et al., (1992), as cited by IPCS (2005)]. To determine a 'safe level', a safety factor of 10 was usually factored on the minimum 'No Observed Adverse Effect Level' (NOEL). However, a brief literature search conducted by the OCM appeared to support the limit of 0.02% for total alkaloids, as proposed by the MCC.
- The OCM suggested that if the scheduling would be based on a maximum alkaloid amount, then it should not be necessary to also put restrictions on the herb itself, nor the pack size. This would significantly simplify the wording of the proposed scheduling. For example:

  Prescription: Aconitum spp; except when specified elsewhere in this schedule.
  Pharmacy only: Oral or dermal preparations of Aconitum spp containing 0.02% or more of total alkaloids.
  General sale: Oral or dermal preparations of Aconitum spp containing less than 0.02% of total alkaloids.

- For information, the following *Aconitum* species were included on the Australian Register of Therapeutic Goods (ARTG) either in homoeopathic potencies (ranging from 4X to 15 X), or in Chinese medicines in minute quantities:

  - *Aconitum carmichaeli*

5 medicines on the ARTG [4 medicines in quantities ranging from 15.6ng to 10 microgram and also 1 grandfathered medicine listed as a 1:35.5 extract (the latter medicine would be further investigated by the OCM)].

  - *Aconitum kusnezoffi*

7 medicines on the ARTG (in quantities ranging from1ng to 10 microgram).

  - *Aconitum napellus*

33 homoeopathic medicines on the ARTG (in potencies of 4X to 15 X), and in one multi ingredient Chinese medicine in the quantity of 1 microgram.

Members noted that the evaluator of XXXXXXXX submission also recommended that "*For topical aconite-containing preparations, it is suggested that a clear warning be printed on the labelling of all such products, stating that the preparation should not be applied to wounds or abraded surfaces*".

A member indicated that the concentration of aconite in dermal preparations was quite low and therefore the proposed warning statement would be unnecessary. Furthermore, the member indicated that from a regulatory point of view, there was no mechanism available in New Zealand to enforce mandatory label requirements as a condition for exemption unlike Australia where it had the ability to enforce reverse scheduling provisions. On this basis, New Zealand would be unable to harmonise with schedule entries where the exemption of a substance from scheduling relied on compliance with label requirements. The member advised that general sales products in New Zealand were classified as dietary supplements and that as such there were no mechanisms available for placing restrictions on such products under the current New Zealand legislation.

Members discussed the option of including an age restriction on medicines noting that the maximum pack size allowed in the proposed S2 entry was the same as the level cited by OCM at which severe poisoning was reported after ingestion of as little as 0.2 mg of the toxic alkaloid aconitine, presumably in an adult. It was noted that this issue was not specifically addressed in OCM's response or by MCC. Members agreed that this matter could be effectively dealt with at registration when products become available but also agreed to seek comment from OCM on the issue of use of aconite preparations in children for consideration at the June 2006 meeting.

DECISION 2006/46 - 1

The Committee agreed to confirm the foreshadowed decision on the grounds of harmonisation.

Schedule 2 – New entry

ACONITUM spp:

ACONITUM spp:

(a) in preparations for oral use in packs each containing 0.2 milligrams or less of total alkaloids **except** in packs containing 0.02 milligrams of total alkaloids; or

(b) in preparations for dermal use containing 0.02 per cent or less of total alkaloids, in packs each containing 0.2

milligrams or less of total alkaloids **except** in packs containing 0.02 milligrams of total alkaloids.

Schedule 4 - Amendment

ACONITUM - amend entry to read:

ACONITUM spp **except**:

(a) when included in Schedule 2;

(b) in preparations for oral use in packs containing 0.02 milligrams or less of total alkaloids; or

(c) in preparations for dermal use containing 0.02 per cent or less of total alkaloids in packs each containing 0.02 milligrams or less of total alkaloids.

1.8.1.2.2 ACRIVASTINE, AMIDOPYRINE AND ATOSIBAN

The Committee noted that acrivastine, amidopyrine and atosiban were classified Prescription medicines in New Zealand but were unscheduled in Australia. In order to harmonise with New Zealand the October 2005 NDPSC meeting agreed to Committee foreshadow the decision to include these substances in S4 of the SUSDP.

There were no products on the ARTG containing these compounds therefore there was no expected regulatory impact on therapeutic products.

The Committee noted that no public submissions had been received.

DECISION 2006/46 - 2

The Committee agreed to confirm the foreshadowed decision on the grounds of harmonisation.

Schedule 4 - New entries

ACRIVASTINE.

AMIDOPYRINE.

ATOSIBAN.

1.8.1.2.3 AMOROLFINE

Members noted that in Australia, the primary entry for amorolfine was in S4 and preparations for topical use were S3 except those containing 0.25% or less of amorolfine which were S2. The scheduling of amorolfine was unharmonised mainly because of preparations for the treatment of *tinea pedis* which were General Sale medicines in New Zealand while in Australia these were subject to the concentration cut-offs specified in the schedule entries. However, the June 2005 NDPSC meeting agreed to exempt from the requirements of scheduling certain antifungal agents indicated for the treatment of *tinea pedis* to harmonise with New Zealand but these did not include amorolfine. There were no products for the treatment of tinea pedis found on SMARTI or ARTG containing amorolfine at the time.

The October 2005 NDPSC meeting noted that there were no significant safety issues identified from Australian adverse reaction reports associated with the use of amorolfine topical cream products on the nails or on the foot. On the basis of the substance's safety profile, the Committee agreed to foreshadow a decision to harmonise the scheduling of amorolfine with New Zealand at the February 2006 meeting.

DECISION 2006/46 - 3

The Committee agreed to confirm the foreshadowed decision on the grounds of harmonisation.

Schedule 2 – Amendment

AMOROLFINE – amend entry to read:

AMOROLFINE for topical use in preparations containing 0.25 per cent or less of amorolfine **except** in preparations for the treatment of tinea pedis.

Schedule 3 – Amendment

AMOROLFINE – amend entry to read:

AMOROLFINE for topical use **except**:

(a) when included in Schedule 2; or

(b) in preparations for topical use for the treatment of tinea pedis.

Schedule 4 – Amendment

AMOROLFINE – amend entry to read:

AMOROLFINE **except**:

(a) when included in Schedule 2 or 3; or

(b) in preparations for the treatment of tinea pedis.

1.8.1.2.4 AMPHOTERICIN

The Committee noted that amphotericin was S4 in Australia but in New Zealand, it was classified Restricted Medicine for the treatment of oral candidiasis and Prescription Medicine for all other uses. A member advised the October 2005 NDPSC meeting that the MCC would be reconsidering the scheduling of amphotericin at the November 2005 meeting. It was stated that the XXXXXXXX in New Zealand objected to the MCC's recommendation to reclassify amphotericin in lozenges for the treatment of oral candidiasis from Restricted Medicine to Prescription Medicine on the basis that due process was allegedly not observed in the consultation process. The Committee was to be advised of the outcome of MCC's consideration.

The Committee was advised that the MCC held an out-of-session meeting in December 2005 for which the agenda included amphotericin. However, this meeting again deferred further consideration of this matter to the next MCC meeting which was expected to be held sometime in May 2006.

OUTCOME

Members noted that this matter was not included in the NDPSC February 2006 pre-meeting gazette notice and agreed to defer further consideration of the harmonisation of the scheduling amphotericin to await the outcome of MCC's consideration.

1.8.1.2.5 ANTIMONY ORGANIC COMPOUNDS

BACKGROUND

The October 2005 NDPSC meeting noted that the nomenclature in Australia for antimony organic compounds in S4 was unharmonised as New Zealand's Part I entry covered all antimony compounds including inorganic forms. Both countries allowed the same exemption at 1 mg/kg (L). Members at the meeting agreed that the S4 entry should be amended to read 'Antimony for therapeutic use except when separately specified in these Schedules' and further agreed to consider the requirement for a policy on the incorporation of Appendix G exemptions into the SUSDP Schedules at the February 2006 NDPSC Meeting.

DISCUSSION

The Committee noted that a brief review of open literature by the Secretariat suggested that antimony was not a recognised essential mineral or trace element for the human

body. A search of the ARTG showed a number of Listed medicines containing antimony in both organic and inorganic forms while no products were found on SMARTI. Comment had been sought from the OCM on the proposal to include inorganic forms of antimony in S4 to harmonise with New Zealand. Additionally, OCM was requested to notify the Committee if it became aware of potential products which may be affected if the NDPSC confirmed the foreshadowed decision.

Members noted the response from OCM which stated the following:

- The ARTG records showed the following entries for Antimony:

  - **Antimony**
    - One Listed homoeopathic medicine for topical use, containing 10 mg/g of 3X Antimonum crudum.

  - **Antimony potassium tartrate**
    - One Registered medicine for Intravenous administration, containing 1.539 mg/mL.
    - 8 Listed homoeopathic medicines, containing up to 111.111 microlitre/mL.

  - **Antimony trisulfide**
    - 3 Listed homoeopathic medicines, containing up to 142.857 microlitre/mL.
    - One Registered intradermal medication containing 1.1 mg/mL.

- The OCM could only identify homoeopathic Listed medicines on the ARTG containing Antimony and the impact of this harmonisation initiative was therefore likely to be minimal.

The Committee noted that no public submissions had been received.

DECISION 2006/46 - 4

The Committee agreed to confirm the foreshadowed decision on the grounds of harmonisation.

Schedule 4 - Amendment

ANTIMONY - amend entry to read:

ANTIMONY for therapeutic use **except** when separately specified in these Schedules.

1.8.1.2.6 ASPIRIN

BACKGROUND

In Australia, aspirin was included in S2 for oral use with an exemption for preparations complying with pack size, dose and label requirements and S4 for preparations for injection or for oral use combined with caffeine, paracetamol or salicylamides or their derivatives. In New Zealand, aspirin was classified Restricted Medicine for slow release and enteric coated forms containing >300 mg/dose and General Sale for all other preparations. A member indicated to the October 2005 meeting that New Zealand was prepared to consider harmonisation with the Australian OTC scheduling and that most products on the New Zealand market were generally of similar pack sizes that 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 XXXXXXXX with regard to the safety of combination aspirin products if rescheduled to OTC status and in particular, specific comment would be also sought on the historical issue of aspirin and renal disease. The Committee agreed to consider this matter at the February 2006 NDPSC Meeting.

DISCUSSION

The Committee noted the following submissions received:

- XXXXXXXX advised that it marketed several brands containing aspirin as an active including XXXXXXXX and that it supported harmonisation on the least restrictive scheduling of aspirin.
- XXXXXXXX supported the proposal to harmonise the scheduling of aspirin with New Zealand and drew attention to the other related entries in the SUSDP, i.e. paracetamol, salicylamide. XXXXXXXX advised that its product containing 500 mg paracetamol combined with 65 mg caffeine, in packs of 20 or less tablets known as XXXXXXXX had been available in New Zealand for over 5 years as General Sales Medicine while larger pack sizes were available as Pharmacy Only medicines.

  XXXXXXXX stated that the extensive data from the UK and New Zealand where paracetamol compounded with caffeine had been available for general sale for 15 and 5 years, respectively, where submitted to the NDPSC in October 2003 to consider harmonisation of schedule with the New Zealand. At that time, an appraisal of the current medical literature confirmed that there was no substantial evidence to support the contention that fixed dose combinations of paracetamol and caffeine were associated with nephropathy. This was further supported by post marketing experience in the UK and New Zealand, two markets with similar scheduling, consumer habits, population demographics and medicines post-marketing

surveillance to that of Australia. Furthermore, analgesics containing caffeine were widely marketed as OTC medicines in 25 countries around the world.

- XXXXXXXX did not offer any comment but asked for an opportunity to provide post-meeting comment as necessary.

The Committee was advised that the issue of abuse of caffeine products by teenagers was brought to the attention of the Secretariat by a member of the public. To harmonise the scheduling of aspirin with New Zealand, members noted that aspirin combination and immediate-release products containing 300 mg or less of aspirin would become General Sale and that the issue of potential for abuse of caffeine in combination with analgesics warranted further consideration.

The Committee noted that the advice sought from XXXXXXXX had not been received.

OUTCOME

The Committee agreed to refer this matter to the TTHWP for initial consideration and asked that the assessment report of the paracetamol/caffeine combination product submission previously considered by the NDPSC be included in the data package for consideration of the TTHWP.

1.8.1.2.7 ATROPA BELLADONNA AND HYOSCYAMUS NIGER

BACKGROUND

The only difference in the scheduling of *Atropa belladonna* between Australia (S2 and S4) and New Zealand (Pharmacy Only and Prescription) was the exemption in New Zealand of medicines containing ≤300 µg total solanaceous alkaloids/kg (L). The June 2005 NDPSC meeting agreed that the cut-off to exempt hyoscine and hyoscyamine in Appendix G of the SUSDP be amended to 300 micrograms in order to harmonise with New Zealand. However, harmonisation of the cut-offs for the exemption of *Atropa belladonna* and *Hyoscyamus niger* with New Zealand was not considered at the time and remained unharmonised. On this basis, it was agreed at the October 2005 NDPSC meeting that this issue be addressed at the February 2006 meeting to achieve consistency across the solanaceous alkaloid class.

DISCUSSION

The Committee noted the advice from the Joint Agency Establishment Group (JAEG) that the NCCTG had agreed to the recommendation that the exemptions provided in SUSDP Appendix G be integrated back into the substances' schedule entries, where appropriate. JAEG also informed that Appendix G as part of the draft SUSMP would now be blank.

The Committee noted the submission from XXXXXXXX reserving the right to make any additional comments following advice of the outcome of the February 2006 meeting.

DECISION 2006/46 - 5

The Committee agreed to confirm the foreshadowed decision on the grounds of harmonisation.

Appendix G – New entries

ATROPA BELLADONNA (belladonna)	300 micrograms
HYOSCYAMUS NIGER	300 micrograms

1.8.1.2.8 BECLOMETHASONE AND BUDESONIDE

The scheduling of these substances was identified in the database as unharmonised due to the inclusion of a pack size limit of '200 actuations or less' in the S2 entry and the corresponding New Zealand Pharmacy Only entries did not include the condition 'for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over'. To harmonise the scheduling of these substances, the October 2005 NDPSC meeting agreed to consider removing the pack size restriction 'when packed in a primary pack containing 200 actuations or less' from the S2 entry at the February 2006 meeting and to recommend that New Zealand consider specifying the indication and age restriction in the Pharmacy Only entries for beclomethasone and budesonide.

Members agreed that the foreshadowed amendments relating to beclomethasone and budesonide be included under item 18.1 to allow proposed amendments relating to nasal corticosteroids to be considered together.

1.8.1.2.9 BORON/BORIC ACID

BACKGROUND

In Australia, boron was included in S4 for various preparations for human therapeutic use including those for internal use containing more than 3 mg per recommended daily dose, in glycerines and honeys of borax or boric acid, in preparations for vaginal use and in preparations for dermal use containing more than 0.35% of boron except antifungal preparations. In New Zealand, boric acid was Pharmacy Only medicine in preparations containing more than 2% boric acid and General Sale for those containing 2% or less of boric acid. The scheduling of boric acid in New Zealand was noted to have evolved from the need to provide guidance to industry in terms of acceptable product strengths and indications when the issue of toxicity emerged from the use of high strength boron products for the treatment of nappy rash in babies under occlusive conditions. There

were no adverse reactions associated with boron reported in Australia or New Zealand since the year 2000. Harmonising the scheduling of boron with New Zealand would involve rescheduling the primary entry for boron in the SUSDP from S4 to S3. The Committee then agreed that in considering harmonisation of scheduling, it would be appropriate to revisit the scheduling history of the substance to assess whether the historical safety issues associated with boron were still relevant. Furthermore, the Committee requested the Secretariat to assess the potential regulatory impact of the proposal to harmonise the scheduling of boron with New Zealand and agreed to consider the matter at the February 2006 NDPSC Meeting.

The last consideration of boron/boric acid in New Zealand, based on the information available on the Medsafe website, was in November 2000 where the MCC recommended that the NDPSC review its current position on the classification of boron in the light of the 1999 UK draft Review of Boron. This recommendation was taken up by the NDPSC and this Committee reviewed the scheduling of boron at its May 2001 meeting. The NDPSC subsequently agreed to revise the boron S4 entry to exempt a daily oral dose of 3 mg in line with the recommendations of the literature reviewed at the time[1] and to exempt dermal preparations containing 0.34 per cent or less of boron to harmonise with the New Zealand scheduling of dermal preparations. However, the Committee at that time was not prepared to harmonise on the other preparations. The scheduling outcome was accordingly recommended to MCC for consideration but it appeared this recommendation was not considered by MCC.

A review of products on SMARTI for assessment of regulatory impact if New Zealand harmonised with Australia yielded 7 eye preparations (5 GS and 2 Pharmacy Only) and one General Sale vaginal gel containing 9 mg/g boric acid. These products listed boric acid as “other” ingredient which suggested that boric acid may be present as an excipient in these preparations. The concentrations of boric acid in these eye preparations ranged between 6-18 mg/mL. Eye preparations containing boron as active ingredient at any concentration were S4 in Australia but boron when present as an excipient in medicines was excluded from the SUSDP. Furthermore, boron in dietary supplements in New Zealand could not be assessed for regulatory impact as there was no database for such products available for review by the Secretariat.

Both boron and boric acid were listed ‘ingredients’ on the ARTG.

DISCUSSION

Members noted that from an Australian perspective, potentially affected products would move to less restrictive schedules if the Committee were to agree to harmonise with New Zealand except antifungal preparations which would become subject to concentration cut-offs. On this basis, the expected regulatory impact on Australian products would be minimal.

[1]IPCS Environmental Health Criteria (1998), National Academy of Sciences (December 2000) and the Expert Review on Vitamins and Minerals (1999).

A member advised that New Zealand only had products containing boric acid and that boron was not listed as an ingredient in medicines in New Zealand. In contrast, Australian products included as ingredient either elemental boron or boric acid. The member pointed out that the current scheduling of boron in the SUSDP excluded excipients from the requirements of scheduling and that this may need to be reviewed on the basis of the substance's toxicity.

OUTCOME

The Committee agreed to recommend that New Zealand consider harmonising with the scheduling of boron and for MCC to consider making a recommendation to the NDPSC to harmonise on an appropriate nomenclature for boron.

1.8.1.2.10 CAMPHORATED OIL

BACKGROUND

In Australia, camphorated oil for therapeutic use was included in S4 except in admixtures and essential oils when packed and labelled according to SUSDP S5 requirements. In New Zealand, camphorated oil was Prescription Medicine for all preparations. The October 2005 NDPSC meeting noted that the rationale behind the Australian exemption for admixtures containing camphorated oil was not available from old NDPSC minutes reviewed by the Secretariat. To progress harmonisation of scheduling, it was then agreed that the potential regulatory impact of the proposal to harmonise with New Zealand be assessed prior to consideration of this item at the February 2006 NDPSC Meeting and that a definition for "admixture" be included in the agenda papers.

DISCUSSION

The Committee noted the advice received from OCM on the proposal to harmonise with the New Zealand scheduling for camphorated oil. The OCM advised that:

- "Camphorated oil" was not included as an allowable ingredient on the ARTG. The OCM understood that "camphorated oil" may not be on the ARTG as an ingredient because the name referred to a formulated product.
- The OCM did not hold information on the precise composition of camphorated oil, although a brief examination of electronic sources revealed that, historically, it consisted of between 11 and 20% camphor made up in cottonseed oil. It was also noted that, because of its high toxicity and association with many cases of poisoning, it had been banned in some countries.
- There is no monograph for "camphorated oil" in the current BP. However, the OCM noted an obsolete monograph for it in the BP 1973. The BP 1973 monograph is

called “Camphor Liniment”, which is a synonym for "Camphorated oil". It defines the product as a mixture containing camphor (20% w/w) and arachis oil.

- Other chemistry references have slightly different definitions of "camphorated oil". For example, "Hackh's Chemical Dictionary" from 1944 defines "camphorated oil" as:

  Camphor liniment. A mixture of 1 pt. camphor and 4 parts cottonseed or olive oil. Used as rubefacient.

- Based on the above, the OCM considered that the broadest legal definition would be that it consists of a mixture of camphor (11-20% w/w) in a vegetable oil.
- The OCM could not be certain as to what the “admixtures” referred to in the SUSDP are, and why they should be excluded from S4, given that the mixture would still contain camphor.
- Given that “camphorated oil” is not defined in the current BP and is not an accepted ingredient on the ARTG, perhaps the NDPSC can consider any Schedule 4 entries for formulations containing camphor to be based on the total amount of CAMPHOR in that preparation. A safety assessment may need to be conducted to provide an estimate of what the value for the minimum concentration of camphor should be. There may need to be some consequential amendments to the other entries for camphor in the SUSDP.
- Whilst there were no products on the ARTG containing “camphorated oil” as an ingredient, there were products on the ARTG containing “camphor oil”, “camphor oil white” and “camphor oil brown,” . However, the precise identity of these ingredients, and their equivalence with camphorated oil remained uncertain. “Camphor oil white” and “camphor oil brown” are oils derived from the wood of *Cinnamomum camphora* (camphor laurel). The two names are AANs and are defined in the BPC 54. “Camphor oil white” is synonymous with “rectified camphor oil”. “Camphor oil white” and “camphor oil brown” are different fractions of the essential oil, from which most of the camphor has been removed. The TGA cannot be certain about the definition for “Camphor oil” as it is not an AAN - but it is presumed that it is closely related to “camphor oil white” and “camphor oil brown”.
- The impact of this proposed harmonisation initiative is difficult to anticipate at the present time.

The Committee noted the pre-meeting submission received from XXXXXXXX which raised the following points:

- it was unclear as to whether NDPSC had considered new information that raised concerns with regard to essential oils or admixtures or whether any ADRAC or other information had prompted concerns;
- an agreed definition for “admixture” would be welcomed; and

- whilst the differences between Australia and New Zealand were noted it was understood that, as a principle, the least restrictive regulatory intervention should apply unless there was evidence to support a more restrictive position. It is also important to recognise that the population (and hence per capita market) in New Zealand is approximately 20% of that of Australia.
- XXXXXXXX would welcome further dialogue with NDPSC in being able to progress industry comment on this Agenda Item. XXXXXXXX is an interested party and stakeholder with regard to this item and would appreciate being advised of the Committee's consideration, with the opportunity for further submission, if appropriate.

A pre-meeting submission had been received from XXXXXXXX indicating interest on this item, particularly in relation to the definition of admixture.

A member advised that camphorated oil was commonly prescribed by doctors in New Zealand.

The Committee noted that the amount of camphor was already restricted by virtue of the scheduling of camphor in S5 and S6 of the SUSDP and that removing the exemption for 'admixtures' from the existing S4 entry for camphorated oil and limiting the S4 camphorated oil entry to therapeutic uses only should clarify the scheduling intent and achieve harmonisation with New Zealand.

DECISION 2006/46 - 6

The Committee agreed to confirm the foreshadowed decision on the grounds of harmonisation.

Schedule 4 – Amendment

CAMPHORATED OIL – amend entry to read:

CAMPHORATED OIL for therapeutic use.

1.8.1.2.11 CATHINE

BACKGROUND

Cathine, a psychoactive constituent of the Khat shrub, was included in S4 in Australia but was not classified as medicine in New Zealand. There were no products containing cathine found on either ARTG or SMARTI. The Committee noted that the TTHWP Meeting 14 recommended that cathine be rescheduled to S9 based on abuse potential and on the grounds that cathine was not a recognised therapeutic ingredient. Members agreed to consider the proposal to reschedule cathine to S9 at the February 2006 NDPSC

Meeting while noting that the TTHWP also made a recommendation to the MCC to consider recommending the inclusion of cathine in the Misuse of Drugs Act (MODA). Advice had been sought from Treaties and Monitoring Section and from all jurisdictions to identify any issues which may be of concern if the Committee agreed to reschedule cathine to S9.

DISCUSSION

The Committee noted that Treaties and Compliance Section of the TGA made a submission to the NDPSC and raised the following points for consideration:

- Cathine, which is included in Schedule III of the United Nations' Convention on Psychotropic Substances, 1971, is subject to import control under Regulation 5 of the Customs (Prohibited Imports) Regulations 1956 and to export control under Regulation 10 of the Customs (Prohibited Export) Regulations 1958. This requires that a prospective importer or exporter of this substance is required to hold a licence and permit to import or export for each shipment.
- This level of import and export control under Australian Customs legislation is applied to all substances in Schedules I, II, III and IV of the 1971 Convention, and this includes substances that are included under Schedule 4, 8 or 9 of the SUSDP. Thus rescheduling of Cathine from Schedule 4 to Schedule 9 of the SUSDP would have no impact on the level of import or export control currently imposed on this substance.
- Cathine is a constituent in the leaves of the Khat (*Catha Edulis*) shrub which is frequently imported for personal recreational use mainly into New South Wales and Victoria by **[**remainder of sentence deleted**]**. Possession of Khat in Western Australia and South Australia is currently prohibited on the basis of this plant containing cathinone, a substance included in Schedule 9 of the SUSDP. In considering the abuse potential of cathine as a basis for rescheduling of cathine from Schedule 4 to 9 of the SUSDP the Committee may thus wish to consider the impact of rescheduling of this substance on the way in which possession of Khat is treated by individual States and Territories.

The Committee noted that no public submissions were received.

Members noted that rescheduling cathine to S9 would not have a significant impact on the import regulation of cathine into Australia given that the same controls were applied on Schedule 4, 8 or 9 substances in the SUSDP. Jurisdictional members expressed a view that the existing controls specified under individual State/Territory poisons legislation were adequate and addressed the specific needs of each jurisdiction.

OUTCOME

The Committee agreed that the scheduling of cathine remained appropriate and to recommend that New Zealand consider harmonising with the S4 classification of cathine.

1.8.1.2.12 CEPHACETRILE, CEPHALORIDINE, CEPHAMANDOLE AND CEPHAPIRIN

This matter is dealt with under item 21.1.1 of the agenda.

1.8.1.2.13 CEPHAZOLIN

This matter is dealt with under item 21.1.1 of the agenda.

1.8.1.2.14 DIBROMPROPAMIDINE AND PROPAMIDINE

BACKGROUND

The October 2005 NDPSC meeting noted the MCC June 2005 meeting's proposal that both countries should have a parent entry in S4 for propamidine and dibrompropamidine and that eye preparations should be included in S2. The advice received from the MCC Secretary indicated that the MCC at its June 2005 meeting agreed to include the two compounds in Part I (S4) and the MCC confirmed that the Pharmacy status of products for ophthalmic use in New Zealand remained appropriate on the grounds that it would not be appropriate for antibacterial eye products to be sold as General Sales medicines. Both substances were exempt in Australia as dibrompropamidine was covered by the SUSDP Appendix B entry for propamidine. There were no specific safety issues raised by the MCC.

The October 2005 NDPSC meeting agreed to foreshadow a recommendation that Australia harmonise with the New Zealand scheduling for propamidine and dibrompropamidine. The October 2005 NDPSC meeting also noted what appeared to be an inappropriate 'reason for entry' for propamidine in Appendix B, i.e. for industrial use only, while the 'area of use' specified was 'Human therapeutic use – Eye Drops'.

The safety of propamidine isethionate eye drops 0.1%, 10 ml and dibromopropamidine isethionate eye ointment 0.15% was last reviewed by the NDPSC in 1992 where the ADEC recommended that both compounds remain unscheduled as they had been for many years, provided the products were labelled appropriately. No other products appeared to have been considered by the NDPSC since then.

The Centre for Adverse Reactions Monitoring (CARM) had advised that three reports had been received for propamidine isethionate and two reports for dibrompropamidine in New Zealand. Of the three reports for propamidine: one was associated with topical use (contact dermatitis) and two with ophthalmic use (conjunctivitis and local site reaction/dysaesthesia). Both cases for dibrompropamidine were topical administration resulting in contact dermatitis.

The February 2000 NDPSC meeting noted propamidine and dibrompropamidine were included in Part III in New Zealand, but were not scheduled in Australia. In accordance with the principles of harmonisation and because there were no public health issues identified in Australia at the time, deletion from Part III was recommended. This recommendation had not been taken up by New Zealand and separate entries for both medicines in Part III and Part I had been retained.

The search for products yielded one eye-drop product containing 1mg/mL propamidine isethionate for supply in Australia registered on the ARTG and only one discontinued antiseptic topical cream 0.15% was found on SMARTI. No products containing dibrompropamidine was found on the ARTG but two products containing dibrompropamidine isetionate, 0.1% eye drops and 0.15% eye ointments, were found on the SMARTI database. The Committee noted five adverse reports relating to XXXXXXXX received in Australia which included conjunctival ulcer, conjunctivitis, ocular/conjunctival hyperaemia and eye swelling. The Committee agreed to review the inclusion of propamidine in Appendix B in conjunction with the New Zealand proposal.

DISCUSSION

The Committee was advised that the sponsor of XXXXXXXX had been invited to comment on the proposal to harmonise the scheduling of dibrompropamidine and propamidine with New Zealand. However, no response was received from the sponsor and no submissions were received from the public.

Members did not support the option of listing the parent entry in S4 for dibrompropamidine and propamidine to harmonise with New Zealand while exempting only ophthalmic preprarations. Members maintained the view that the exemption provided for ophthalmic preparations in Appendix B of the SUSDP did not imply that other preparations were scheduled and that harmonisation on the least restrictive scheduling would require New Zealand to reclassify the Part I (S4) entries for dibrompropamidine and propamidine to General Sales.

A member advised that New Zealand would support harmonisation on the least restrictive scheduling on the basis that there were no significant safety issues noted with ophthalmic use of dibrompropamidine and propamidine. Whilst it was recognised that New Zealand did not have an existing mechanism for picking up exemptions specified in Appendix B, harmonised regulatory outcomes could be achieved by classifying substances to General Sale medicines in New Zealand.

DECISION 2006/46 - 7

The Committee agreed to recommend that New Zealand consider harmonising with the scheduling status of dibrompropamidine and propamidine.

Furthermore, the Committee agreed to include a new entry for dibrompropamidine in Appendix B for clarity and amend the entry for propamidine in Appendix B to correct the reason for listing from 'industrial use only' to 'low toxicity'.

APPENDIX B – Amendment

PROPAMIDINE - amend entry to read:

PROPAMIDINE	Nov 1992	a	6.10

APPENDIX B – New entry

DIBROMPROPAMIDINE	Feb 2006	a	6.10

1.8.1.2.16 MERCURY ORGANIC COMPOUNDS

BACKGROUND

In Australia, the parent entry for mercury for therapeutic or cosmetic use, except when in a sealed device which prevented access to mercury, was in S4 while preparations for topical human therapeutic use containing ≤ 0.5% of mercury organic compounds were in S2. The scheduling of mercury was 'essentially' harmonised with New Zealand except for the nomenclature adopted in S2, i.e. mercury organic compounds vs. mercury (New Zealand). This meant that all medicines containing inorganic compounds of mercury were S4 in Australia while in New Zealand, preparations containing organic or inorganic forms of mercury for external use containing 0.5% or less of mercury were classified Pharmacy Only medicines and all other preparations were prescription medicines except those containing 1 mg/kg (L) of mercury (also specified in Appendix G of the SUSDP). A search of the ARTG showed a number of Listed medicines containing mercury. Advice was sought from OCM on the proposal to harmonise with New Zealand and on the potential regulatory impact if the Committee confirmed the foreshadowed decision.

DISCUSSION

The Committee noted that OCM had advised that:

- There were five medicines listed on the ARTG with mercury as an ingredient. Four of these medicines were for dental use and 1 product was an oral homoeopathic medicine.
- There should be no impact of this proposal on medicines currently listed on the ARTG.

No public submissions were received.

DECISION 2006/46 - 8

The Committee agreed to confirm the foreshadowed decision to harmonise with New Zealand.

Schedule 2 - Amendments

MERCURY – amend entry to read:

MERCURY for external use in preparations containing 0.5 per cent or less of mercury.

1.8.1.2.17 PIRFENOXONE SODIUM (CATALIN)

This matter was dealt with under item 21.1.2 of the agenda.

1.8.1.2.18 BLOOD PRODUCTS

The scheduling of fractionated blood products including antithrombin and blood clotting factors was deferred at the October 2005 NDPSC until input from the NBA's Jurisdictional Blood Committee on the possible ramifications of scheduling fractionated blood products and recombinant blood products was received. There was no further action required on this matter until the final outcome of NDPSC consideration is known. See agenda item 11.4.

1.8.2.1 OUTCOMES OF THE TTHWP MEETING 15 (CYCLIZINE AND RECOMBINANT MEDICINES NOMENCLATURE)

The TTHWP at its meeting held on 20 February 2006 (Meeting 15), considered two items on the agenda, i.e. cyclizine which was referred by the NDPSC to the Working Party, and nomenclature of recombinant medicines. The outcomes of the Working Party's consideration were put forward for consideration of the NDPSC at its meeting held on 21-23 February 2006.

1.8.2.1.1 CYCLIZINE

PURPOSE

The Committee considered the TTHWP Meeting 15 recommendation in relation to cyclizine.

BACKGROUND

Members recalled that retaining travel sickness products containing a sedating antihistamine in S2 allowed the sale of such products in premises licensed by the jurisdictions, e.g. truck stops, ferry terminals, airports, etc., as the poisons legislation in most States and Territories did not include provisions for allowing licensed sellers to dispense S3 medicines except by a pharmacist or healthcare practitioner. On this basis, the Working Party was of the view that there was merit in retaining travel sickness products in S2, where there were products in Australia and/or New Zealand, and the rest may be included in S3, particularly cyclizine where reports of abuse had been received. In effect, this approach exempted travel sickness products from the harmonisation principles set out in TTHWP Decision 8/8, which recommended that single-active preparations of sedating antihistamines be included in S3/Part II.

The Committee noted in the June 2005 MCC minutes that cyclizine for the treatment of travel sickness was reclassified from Pharmacy Only to Restricted Medicine in New Zealand as part of the rescheduling of single-active preparations containing sedating antihistamines and on the basis of its abuse potential. A member advised that cyclizine was reported by pharmacists and drug abuse agencies in New Zealand as being the sedating antihistamine of choice by opiates users. There were no products containing cyclizine registered on the ARTG at that time and all cyclizine preparations were Prescription Only medicines in Australia. The October 2005 NDPSC meeting agreed that it was appropriate to refer the scheduling of cyclizine to the February 2006 TTHWP meeting for initial consideration of harmonisation.

A search of the ARTG suggested that there were travel sickness products in both Australia and New Zealand containing dimenhydrinate and promethazine. New Zealand also had a listing in SMARTI for travel sickness products in S2 containing meclozine XXXXXXXX and whilst no travel sickness products appeared to be listed on SMARTI, the MCC had advised that there was a Pharmacy Only medicine registered in New Zealand.

Substance	Products in S2/Pharmacy Only	
	Australia	New Zealand
Cyclizine	none	1 (S3)
Diphenhydramine	none	none
Dimenhydrinate	several XXXXXXXX	Several XXXXXXXX
Meclozine	None	1 XXXXXXXX
Promethazine	1 XXXXXXXX	1 XXXXXXXX

DISCUSSION

The Committee noted the following options from the TTHWP Meeting 15:

Option 1: Retain all sedating antihistamines for travel sickness in S2 except for cyclizine which the NDPSC may wish to consider rescheduling to S3 to harmonise with New Zealand (cyclizine was included in S4).

Option 2: Retain sedating antihistamines in travel sickness products except for cyclizine where there were products on the market in either Australia or New Zealand in S2. Those substances without registered products, i.e. diphenhydramine, should be rescheduled to S3.

The Committee supported Option 1 and noted that there were no abuse issues identified with the travel sickness products except for cyclizine. Furthermore, jurisdictional members maintained their support for the continued availability of small packs of travel sickness products in locations such as truck stops, ferry terminals and airports. The members advised that majority of the jurisdictions did not have a mechanism to allow such supply to occur if the products were rescheduled to S3. It was accepted that cyclizine should be included in S3 rather than S2 due to the abuse concerns.

The Committee noted XXXXXXXX submission asking to be kept informed of any outcomes and the opportunity to provide comment during the post-meeting period should specific issues arise.

DECISION 2006/46 - 9

The Committee agreed to reschedule cyclizine in travel sickness products to S3 while retaining the primary entry in S4 to harmonise with New Zealand.

Schedule 3 – New entries

CYCLIZINE in preparations for oral use.

Schedule 4 - Amendments

CYCLIZINE – Amend entry to read:

CYCLIZINE **except** when included in Schedule 3.

1.8.2.1.2 RECOMBINANT MEDICINES

PURPOSE

The Committee considered the TTHWP Meeting 15 recommendation in relation to recombinant medicines.

BACKGROUND

The Working Party was informed that the advice sought from XXXXXXXX on the proposed amendment in Part 1 of the SUSDP was not received. To progress this matter, the Working Party agreed to include this item on the agenda of the NDPSC and recommend that a decision be foreshadowed on the basis of the proposed Part 1 wording for recombinant medicines proposed by the Secretariat.

DISCUSSION

The Committee was advised that following the TTHWP 15 meeting, advice was received from XXXXXXXX supporting the inclusion of a provision in SUSDP Part 1 to cover the scheduling of every recombinant form of a substance. Furthermore, XXXXXXXX noted that the wording proposed to the TTHWP was appropriate. The Committee noted the XXXXXXXX advice which stated that:

[Paragraph deleted**]**

A member expressed concern on the potential regulatory impact of the proposed Part 1 amendment on non-therapeutic products. The Committee agreed to foreshadow the amendment and publish notification of the Committee's intent to consider this matter in the June 2006 pre-meeting gazette notice to allow public comment.

OUTCOME

The Committee agreed to foreshadow the decision below to include a provision in Part 1 of the SUSDP which would cover all recombinant variants of parent molecules listed in the Schedules.

FORESHADOWED DECISION (for consideration at the June 2006 Meeting).

Part 1 Interpretation – Amendment

Paragraph 1. (2) – Amend entry [to include a new subparagraph (f)] to read:

(a) that substance prepared from natural sources or artificially; and

(b) where the substance is a plant (other than a plant included in Schedule 8 or 9), that plant or any part of that plant when packed or prepared for therapeutic use; and

(c) every salt, active principle or derivative of the substance, including esters and ethers, and every salt of such an active principle or derivative; and

(d) every alkaloid of the substance and every salt of such an alkaloid; and

(e) except where the substance is levomethorphan or levorphanol, every stereoisomer of the substance and every salt of such a stereoisomer;

(f) every recombinant form of the substance; and

(g) a preparation or admixture containing any proportion of the substance, but does not include:

(h) a preparation or product included in Appendix A, or a substance and the reason for its entry in Appendix B; or

(i) a substance included in Appendix G at a concentration not exceeding the concentration specified in column 2 of that Appendix in respect of that substance; or

(j) 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 also included in Schedule 7 or 8.

(k) any substance present as an impurity in a pesticide, at a concentration at or below the maximum content for that substance, specified for the pesticide in the current version of the *Minimum Compositional Standards (MCS) for Active Constituents* or its successor, as published by the Australian Pesticides and Veterinary Medicines Authority.

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

2.1 SUSDP, PART 1

No items were considered.

2.2 SUSDP, PART 2

2.2.1 APPROVED NAME FOR AMINES USED AS CURING AGENTS FOR EPOXY RESINS

PURPOSE

The Committee considered an inconsistency regarding the SUSDP approved name of amines used as curing agents for epoxy resins where the amine was an aromatic amine.

BACKGROUND

At the August 1967 Poisons Scheduling Committee (PSC) Meeting the Committee agreed that, as the main hazard associated with epoxy resins was the dermal toxicity of the hardeners and reactive diluents, a new entry in Schedule 5 was warranted which read "Liquid epoxy resins and all amines and organic anhydrides used as curing agents for epoxy resins". This was refined at the March 1968 PSC Meeting to read "Epoxy resins and their curing agents and hardeners".

At the November 1988 Drugs and Poisons Scheduling (Standing) Committee (DPSSC) Meeting the Committee agreed to separate the curing agents from the epoxy resins and thus to create a Schedule 5 entry for "epoxy resins, liquid" and Schedule 5 entries for the two classes of curing agents for epoxy resins: "anhydrides, organic" and "amines".

Following the August 1994 NDPSC Meeting Members noted advice from the Drafting Advisory Panel that it would be adequate to label the content of a product containing a mixture of epoxy resins as the proportion of "liquid epoxy resins" and for a product containing a mixture of amines for curing the resins as the proportion of "aliphatic amines". The NDPSC agreed, out-of-session, to implement this advice by adding the current epoxy resin and amines entries to the Table under subclause 7(1)(k)(iii). There appeared to have been no consideration given to the situation where an amine for curing epoxy resins was an aromatic amine.

DISCUSSION

The Members were advised that the Secretariat had recently received a request concerning the SUSDP approved name for 2,4,6-tri(dimethyl-aminomethyl)phenol, an aromatic amine, when used for curing epoxy resins. The Secretariat's initial response to

the enquiry confirmed that 2,4,6-tri(dimethyl-aminomethyl)phenol, when used for curing epoxy resins, was captured by the Schedule 5 general entry for "amines". A consequence of this scheduling, however, was that an approved name for amines when used for curing epoxy resins was "aliphatic amines" as set out under Labels and Containers, sub-clause 7(1)(k)(iii).

The Secretariat advised that it had approached Jurisdictional Members in late October 2005 for views and comments regarding the use of the name "aliphatic amines" on a label where the amine was actually an aromatic amine. The response from the XXXXXXXX Member advised that the Secretariat indicate to the enquirer that as the compound was not an aliphatic amine, the general description of "aliphatic amines" should not be used and instead that the full chemical name be used on the label. This view was supported by the XXXXXXXX Member who also suggested that presumably the sponsor had a shorter brand name which it could also use. The XXXXXXXX Member suggested that when the table in 7(1)(k)(iii) was drawn up it was thought that all amines for curing epoxy resins were aliphatic. The XXXXXXXX Member also raised two questions for consideration:

- Was an addition of "aromatic amines" to sub-clause 7(1)(k)(iii) as a general description appropriate, given that this may cover a large number of compounds? The Members noted the Schedule 5 rider of "for use as curing agents for epoxy resins (unless separately specified in the Schedules)" already limited the number of compounds covered.
- While 2,4,6-tri(dimethyl-aminomethyl)phenol fitted within the Schedule 5 entry for "amines" was the toxicity profile of 2,4,6-tri(dimethyl-aminomethyl)phenol consistent with a Schedule 5 listing - given that other amines for curing may all be aliphatic amines was there a need to assess the appropriate scheduling of this aromatic amine?

A Member noted that amines for curing epoxy resins had only ever been looked at as a group, and the toxicity of individual amines in this group did not appear to have been examined by the Committee. The XXXXXXXX Representative offered to recommend to XXXXXXXX that it undertake a review of a range of aromatic amines used for curing agents to see if their toxicity was consistent with a Schedule 5 entry.

The Committee also noted that 2,4,6-tri(dimethyl-aminomethyl)phenol may be captured by the Schedule 6 phenol entry as 2,4,6-tri(dimethyl-aminomethyl)phenol was both a modified amine and a modified cresol.

The Committee agreed that there were two issues, a minor labelling clarification involving the approved name for those amines captured already by the Schedule 5 entry, and the broader issue of the toxicity of aliphatic versus aromatic amines for curing epoxy resins. The Members agreed to defer consideration of the broader issue until XXXXXXXX had undertaken a review.

DECISION 2006/46 - 10

The Committee agreed, so as to clarify an inconsistency, to amend the entry in the primary pack and immediate containers provisions, subclause 7(1)(k)(iii), for aromatic amines when used for curing epoxy resins indication that "aromatic amines" could be used as an approved name in place of "aliphatic amines".

Part 2 – Labels and Containers

Primary packs and immediate containers – Amendment

Paragraph 7.(1)(k)(iii) **–** Amend entry to read:

7. (1)(k)...

(iii) if the poison is a Schedule 5 poison referred to in column 1 of the following table the name opposite thereto in column 2 may be used as the approved name:

TABLE

Column 1	**Column 2**
Alkaline salts	Alkaline salts
Amines for use as curing agents for epoxy resins (unless separately specified in the Schedules).	Aliphatic amines or aromatic amines
Epoxy resins, liquid	Liquid epoxy resins
Hydrocarbons, liquid	Liquid hydrocarbons
Quaternary ammonium ammonium compounds	Quaternary compound(s)

2.2.2 STORAGE STATEMENTS FOR SCHEDULE 5 AND 6 PRODUCTS

PURPOSE

The Committee considered inclusion of a new paragraph in Part 3 of the SUSDP setting out the requirements for retail storage of Schedule 5 and 6 poisons.

BACKGROUND

At the June 2004 NDPSC Meeting the Committee agreed to replace the definitions for child resistant closure (CRC) and child resistant packaging (CRP) with the current definitions and included the current definition for "Non-access Packaging" in the SUSDP. Post-meeting comment from XXXXXXXX arising from the February 2004 NDPSC Meeting addressed issues including that there were differences between the Jurisdictions in the requirements for retail storage of Schedule 5 (and Schedule 6) poisons. The Committee agreed to refer this matter to XXXXXXXX with a view to the development of a uniform approach to the retail storage of these substances.

At the June 2005 NDPSC Meeting the Committee considered a request for advice on the issue of child resistance for products which comply with the definition of "Non-access Packaging" but do not comply with AS1928-2001. The Committee also considered a recommendation from XXXXXXXX to include a paragraph in Part 3 of the SUSDP under the "storage" section relating to the retail storage of Schedule 5 and 6 poisons to enhance national consistency. XXXXXXXX asserted that this would give a clear message to retailers as to the minimum standard that was acceptable for storage of these substances. The Committee agreed to the XXXXXXXX recommendation and further agreed that an additional exception be added to XXXXXXXX recommendation to reflect the existence of the definition for "Non-access Packaging" in the SUSDP.

At the October 2005 NDPSC Meeting the Committee agreed to set aside the June 2005 decision based on post-meeting comment received, and to allow opportunity for further consultation with stakeholders. The Committee also agreed to foreshadow consideration at the February 2006 NDPSC Meeting of a paragraph for inclusion in Part 3 of the SUSDP setting out the requirements for storage of Schedule 5 and 6 poisons in order to enhance national consistency, along the lines of the following:

44a. "A person who sells or supplies a Schedule 5 or Schedule 6 poison in a retail shop must keep those poisons in such a way that, when displayed for sale, they are positioned at least 1.2 metres above the floor except:

- when packed in a container fitted with a child-resistant closure;
- in a container with a capacity of 5 litres/5 kilograms or more;
- packed in child-resistant packaging;
- packed in non-access packaging; or
- a hair dye packed with a volume of 50 millilitres or less.

They must be displayed in such a way to prevent contamination of human or animal food, or beverages should a leak or breakage occur."

DISCUSSION

The Members recalled the following points raised at the October 2005 NDPSC Meeting:

- The Committee generally agreed that there was a strong desire by major retail chains to have a nationally consistent approach to the retail storage requirements for Schedule 5 and 6 products. A Member advised that he had been approached by XXXXXXXX who wished to encourage the NDPSC to implement a set of nationally uniform storage requirements for Schedule 5 and 6 products.
- A Member also inquired whether the label statement "keep out of reach of children", the driver behind the development of a uniform storage statement, was more for the domestic rather than retail setting. However, another Member advised of a poisoning incident where an amount of a Schedule 5 aquarium liquid, displayed on a low shelf, was swallowed by a child. The Member advised that the retailer was informed that storage near the floor was not considered to be "out of reach of children". The Committee generally agreed that the label statement "keep out of reach of children" was appropriate in both retail and domestic settings.

The Committee also recalled the following points raised by the XXXXXXXX submission considered at the October 2005 NDPSC Meeting:

- XXXXXXXX supported the move towards national uniformity but questioned why such a regulatory response in some jurisdictions was not necessary in the past.
- XXXXXXXX asserted that there had not been the opportunity for the ramifications of the change to be fully evaluated by industry for all Schedule 5 and 6 poisons in retail across the possible range of retail outlets; nor to identify specific products that may be forced into packaging changes.
- The proposal may have significant cost implications to industry associated with "buying" shelving/display space in the region of 1.2 m or greater.
- XXXXXXXX recommended that the decision be deferred until there had been opportunity for XXXXXXXX to provide additional information. The Committee was advised at the October 2005 Meeting that, due to a delay in responses from stakeholders, this information would not be available until the February 2006 NDPSC Meeting.

XXXXXXXX in response to XXXXXXXX submission, had noted that:

- all scheduled poisons carry the cautionary statement "KEEP OUT OF REACH OF CHILDREN" and that an entry for storage of Schedule 5 and 6 poisons merely articulates the interpretation of what is considered to be out of children's reach.

- retailers in particular would be pleased to have some indication regarding this issue to assist with liability concerns if children manage to access poisons while in their stores.
- the new paragraph represents a significant advance so that retailers get uniform advice.
- QLD, NSW (for Schedule 6 only) and SA have similar existing requirements.
- a uniform approach will assist retailers and the regulators and that inclusion of the new paragraph is well overdue.

The Members noted a submission from XXXXXXXX. The submission XXXXXXXX was identical to one considered at the June 2004 NDPSC Meeting and contained no new information. One part of the submission addressed the issue of different storage requirements in different Australian jurisdictions (as described in background above).

The Committee considered a submission from XXXXXXXX which raised the following points:

- The proposed new entry would restrict retail sale to positions above 1.2m except if, (amongst others) the containers are fitted with a CRC (in accordance with AS1928).
- In review of AS1928, there is no clear indication of how this can be applied to aerosols.
- The submission questioned whether any consideration had been given to these products in determination of the proposed changes - i.e. are there any exemptions for aerosols, or is it assumed these would be subject to the same storage restrictions?

The Committee also considered a submission from XXXXXXXX opposing the proposed national storage requirements for Schedule 5 and 6 poisons. XXXXXXXX:

- Are particularly opposed to such controls on Schedule 5 products and asserted that this would impact on a wide range of aerosol products, especially spray paints and pest control products.
- Advised that CRP was not readily available for aerosol products and indeed was not applicable for the increasing volume of aerosols which used an integrated actuator.
- Reiterated the cost of requiring products to be displayed above 1.2 m.
- Advised that a number of brands of spray paint have their own proprietary merchandising display racks which are designed to display the full range of colours available. These go to floor level.
- Asserted that the reduced likelihood of accidental ingestion from an aerosol package had been recognised by authorities for some time and had seen products packed in the aerosol format exempted from the requirements for CRP in many jurisdictions.

The Committee noted a submission from XXXXXXXX which proposed that, in the interests of uniformity, the current NSW requirements should be adopted nationally.

The Committee recalled that at the October 2005 NDPSC Meeting the XXXXXXXX Member had noted that the proposed storage statement could potentially see many more Schedule 5 products with CRCs or in CRP because sponsors would be seeking to avoid the additional cost of displaying their product above 1.2 metres from the ground. The Committee was also advised of the wide range of retailers, not just large chains, which store Schedule 5 and 6 poisons. The Committee had therefore agreed to a proposal to allow time for industry to present further information to the Members on the possible ramifications of national storage requirements for Schedule 5 and 6 poisons.

Further to the above, the Members considered a submission from XXXXXXXX opposing the proposed paragraph. XXXXXXXX maintained that there had not been adequate articulation and quantification of 'the problem', at the retail level, to warrant the proposed decision. XXXXXXXX noted that a range of issues and considerations impact upon this item:

- The nature of products and packaging that would be impacted, including:
    - aerosol products, trigger packs providing 'ready to use' products (rather than concentrates) and refills for these packs, products packed as a tube in a box, products packed as tablets within foil within a box, powders packed in tubs and composite packaged products.
- The need for regulation to reflect controls required for contemporary rather than historical packaging. For example the origins for a 50mL limit for exemption of hair dyes?
- Behavioural considerations of an unsupervised child in a retail outlet, anticipated periods of unsupervised activity, circumstances of any incidents that may have occurred.
- Identification of the instances of failures of current regulatory controls in states such as NSW (controls limited to Schedule 6, with certain exemptions) compared with QLD for instance where the regulation applies to all schedules without exemptions, i.e. identification of whether changes to current requirements in a range of states (and significant costs) would lead to tangible improvements in safety.

The Committee agreed that there was a need for a nationally consistent position on retail storage requirements for Schedule 5 and 6 products. A Member advised that, should the current situation of different requirements in different jurisdictions continue, some national retailers had indicated that they would apply the most restrictive requirements nationally because of potential litigation and compliance issues.

The XXXXXXXX Member also advised that, with regard to the proposed storage statement, a national retailer XXXXXXXX had indicated that they were not interested in the proposed exemptions. XXXXXXXX advised the Member that if the requirement

then became store above 1.2 m or the product would need a CRC then XXXXXXXX intended to require everything to be in a CRC. The Committee agreed that having any retailer requiring all Schedule 5 and 6 products to have CRCs contravenes the NDPSC's stated public health policy - CRCs should not appear on products unless there was a real need as doing so would diminish the impact of using a CRC.

The Committee noted that, **[**section deleted**]**, and given the strongly held yet divergent views of some jurisdictions, a full discussion was required. The Members agreed that deferment of this issue until the June 2006 NDPSC Meeting was appropriate as it would allow jurisdictions to consider the legislative implications of various options, including the issues identified in the above submissions.

OUTCOME

The Committee agreed to defer consideration to the June 2006 NDPSC Meeting of a revised paragraph for inclusion in Part 3 of the SUSDP setting out the requirements for storage of Schedule 5 and 6 poisons in order to enhance national consistency. This deferment was to allow time for Members to collect additional information to help resolve certain jurisdictional issues.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

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

No items were considered.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 PARAQUAT

PURPOSE

The Committee considered the scheduling of a new formulation containing paraquat.

BACKGROUND

[Paragraph deleted**]**

The applicant requested a consideration of the scheduling of this formulation of paraquat. Paraquat is listed in Schedule 7 of the SUSDP with no cut-off to lower schedules. Paraquat was only recently (2004) the subject of a review conducted by the Office of Chemical Safety (OCS) under the auspices of the Australian Pesticides and Veterinary Medicines Authority's (APVMA) chemical review program. The poisons schedule for paraquat was re-examined during this time and considered to be appropriate.

OCS supported the registration of the new formulation on human health grounds but had reservations about a Schedule 6 classification.

[Paragraph deleted**]**

Supplementary toxicity data and scientific argument were submitted by XXXXXXXX to address some of the above concerns raised by the NDPSC.

[Paragraphs deleted**]**

DISCUSSION

[Paragraph deleted**]**

The Committee received further supplementary toxicity data and scientific argument by XXXXXXXX to address some of the above concerns raised by the NDPSC (see following Table for summary).

[Table deleted**]**

[Paragraphs deleted**]**

OCS Conclusion and Recommendations to the NDPSC

The Committee noted that from a purely hazard-based perspective and considering all of the supplementary data/information, the OCS does not consider that the applicant has addressed all of the concerns raised by the NDPSC and on this basis can find no grounds to amend its previous recommendation; that is that current Schedule 7 classification for paraquat remains appropriate. In discussion with the OCS, the applicant had previously offered to implement a number of risk mitigation measures as part of good product stewardship to address concerns regarding the possible entry of paraquat into the home garden market (if there were to be a cut-off into Schedule 6). These included (1) XXXXXXXX being sold only through accredited and licensed agricultural resellers (2) the following statement being included on the product label "FOR USE ONLY AS AN AGRICULTURAL HERBICIDE. THIS PRODUCT IS TOO HAZARDOUS TO BE USED IN THE HOMEGARDEN" and restricting the formulation to closed system packaging only to limit the potential for worker exposure; (the minimum pack size would be 20 L), which is not amenable to home garden use.

The OCS has suggested that the NDPSC may also like to consider these measures as part of their reconsideration of the poisons schedule for paraquat.

Public Comment in Response to Gazettal

The Committee received through the public comment procedure, comment from XXXXXXXX. (**Secretary's Note**: The Committee also received, outside the timeframe for public consultation, correspondence from the XXXXXXXX and the XXXXXXXX.)

XXXXXXXX

XXXXXXXX noted that the emetic, XXXXXXXX had been used for more than 30 years in all paraquat formulations and the issues that now appeared to concern the committee had not been discussed. In the history of this product, uncontrolled emesis had not been a problem in emergency treatment - if the concerns are dose related (in terms of XXXXXXXX it was difficult to make direct comparisons but a XXXXXXXX product would not allow a direct "transfer of argument" in terms of a greater effect of a larger dose. This effect, however, could be controlled if excessive response is obtained; XXXXXXXX or XXXXXXXX being used as effective controls for vomiting in a clinical setting.

XXXXXXXX further noted that the applicant proposed to use an increased level of emetic in the lower risk formulation, due to the binding of some of the emetic by the XXXXXXXX formulation. According to XXXXXXXX, from the high dose in human studies this was unlikely to result in uncontrolled vomiting, even at dose rates

considerably higher that one would expect even from deliberate ingestion. Even at the highest dose (8mg, Study 1) of the applicant's submission, there was no uncontrolled vomiting.

XXXXXXXX concluded that it was therefore reasonable to conclude that the risk of uncontrolled vomiting post ingestion of the proposed XXXXXXXX formulation of paraquat was remote and that vomiting was likely to be readily controlled by centrally acting anti emetic drugs.

XXXXXXXX

XXXXXXXX noted that a recent investigation of human exposures to paraquat formulations "in use" and reported to their Emergency Response data base showed that the total number of calls per annum had decreased by more than 50% 1997 to 2005. During this time there were 146 reports which were significant enough for users, the Poisons Information Centre or Doctors to phone the XXXXXXXX line for advice. Of these calls by far the largest exposure was via skin (73 calls) and eye (33 calls) with only 14 regarding ingestion from all sources, accidental and deliberate. Thus, over a period of 9 years only 10.3% of the total exposure reports to the XXXXXXXX Emergency line related to oral exposure, and this included spray mist exposure onto oral tissue.

XXXXXXXX also made the point that, by contrast, Victorian Poisons Information Centre (PIC) reports recorded 22 calls for **all** paraquat and diquat from **all** companies in 2003 and 30 calls in 2004. This represented less than one in a thousand calls to the PIC and was nine times less than the call rate for glyphosate and 44 times less than the call rate for paracetamol. The Victorian Poisons Information Centre, which publishes call numbers annually, made no differentiation in its reports between general enquiries and actual exposure cases, nor did it record deliberate ingestion incidents in their published reports. Thus it was reasonable to assume that the XXXXXXXX reports were at least as, or perhaps even a more accurate of actual exposure ratios since XXXXXXXX reports eliminate the "general enquiry" category. It was also reasonable to assume that the number of XXXXXXXX reports compared to Victorian PIC figures is indicative of actual cases involving XXXXXXXX product. On this basis, it was reasonable to conclude that "poisonings" are 10 times more likely to be related to skin, eye or inhalation/smell than by deliberate or accidental ingestion. Therefore, "in use" safety assessment relating to skin, and eye should be the primary point of consideration. By comparison, the assessment by the OCS to date had focused almost exclusively on ingestion.

XXXXXXXX presented information that highlighted the advantages offered by the XXXXXXXX formulation over existing paraquat formulations in terms of skin and eye irritancy.

XXXXXXXX suggested that, anecdotally, there was a link between the requirement for farmer education on the use of agricultural chemicals through "ChemCert", the "Agsafe" accreditation scheme and other training programs. Probably the most significant change

in the period had been in relation to suicide education in the community – Goldney (2004) reported on the peak in suicide rates, and the effect of education programs. Therefore it did not appear that scheduling per se had resulted in reduction in ingestion risk with paraquat, but that external health policies and programs had had a significant effect.

On the issue of the emetic, XXXXXXXX noted that the NDPSC had raised issues around the need for inclusion of an emetic in paraquat formulations and the level of emetic in the proposed XXXXXXXX formulation. The NDPSC had also raised issues around excessive effects from the emetic that may decrease the effectiveness of emergency treatment, while the recent OCS evaluation has now suggested that there may not be enough emetic to cause vomiting. XXXXXXXX noted that as a signatory to the FAO Code of Conduct, it had no choice internationally but to include an emetic in the preparation. XXXXXXXX agreed with the finding of the OCS that the emetic was unlikely to cause harm and therefore contended that this should not inhibit rescheduling this product to S6.

XXXXXXXX reiterated that it had already offered to commit to a package of stewardship activities (as noted above) that OCS agreed could be examined if the NDPSC was to move to Schedule 6 for XXXXXXXX formulations. It was also proposed that packs of greater than 20L were provided only in closed systems. This was now formally proposed in association with a possible S6 gazettal. In addition, and as a commitment that would be ex-SUSDP but nonetheless binding on the company and potentially enforceable through APVMA as a condition of registration, XXXXXXXX was also prepared to commit to any or all of the following elements of a stewardship program (with the elements to be advised by APVMA) in the event that NDPSC granted this formulation S6 status:

- continued support of the Agsafe accreditation system, including refusal to supply those agents who are in breach of the Code as per the ACCC authorisation,
- the XXXXXXXX emergency line number being prominently displayed on the front face of the XXXXXXXX label so that accurate data on exposure can be kept,
- reporting of the XXXXXXXX emergency calls relating to XXXXXXXX to APVMA,
- reporting of the worldwide Adverse Health Incidents for this formulation as per the EC directive, due in 2008, and to which Australia is a reporting country,
- closed systems for the 20L pack are considered as they become available.

XXXXXXXX proposed the following wording for a Schedule 6 entry:

> *Paraquat, in AC preparations containing 250 g/L or less paraquat dichloride plus* XXXXXXXX *and emetic in packs of 20 litres or more.*

The Committee recalled that an option at the June 2005 meeting was to limit the marketing of the paraquat formulation to large scale closed-system packs of 100 litres or

more. From discussions with XXXXXXXX, it appears that 20 litre packs are not amenable to closed distribution/application systems.

Options Considered by the Committee

The Committee considered that it had two options, viz to maintain the status quo and retain paraquat in Schedule 7 or agree to include paraquat in Schedule 6, possibly under a range of conditions that would assist to mitigate the risk.

By maintaining the status quo, the Committee acknowledged that:

- The XXXXXXXX formulation offers no acceptable level of improved safety to public health and that would allow the substance to be included in Schedule 6.
- The proposed risk mitigation measures are insufficient to reduce the risk.
- It is confirming its policy in regard to the inclusion of an emetic in paraquat formulations, i.e. the NDPSC concluded in 1987 that the emetic XXXXXXXX was ineffective at preventing deaths following poisoning and was therefore not a mandatory constituent of paraquat products in Australia.
- Considers that the absence of poisoning incidents involving paraquat is directly linked to the current level of regulatory control.

Alternatively, by agreeing to include paraquat in Schedule 6, the Committee would be acknowledging that:

- The XXXXXXXX formulation provides a degree of additional safety not available in current formulations in the marketplace.
- The supporting data are consistent with paraquat (in an XXXXXXXX formulation with the inclusion of an emetic) being included in Schedule 6.
- The Committee's existing policy in regard to the inclusion of an emetic is being rescinded.
- The Committee now considers that XXXXXXXX is an effective emetic for paraquat poisoning.
- The Committee's existing policy in regard to emesis as a first-aid treatment for pesticide poisoning is being rescinded. (The use of ipecac has been removed from the FAISD).
- The proposed risk mitigation measures are sufficient to reduce the risk to a level consistent with a Schedule 6 substance.
- A Schedule 6 classification is likely to result in more widespread use both in terms of numbers of users and product volume.
- A Schedule 6 classification based largely on risk mitigation measures may set a precedent for other Schedule 7 poisons.

A Committee member had independently reviewed the toxicology (in particular the XXXXXXXX studies) and summarised his conclusions. He suggested that the company had presented a good argument why the lung lesions in the dog had been discounted. He also noted that the company was prevented from more extensive testing because of ethical considerations in the use of animals and the constraints that had therefore been placed on the number of animals that could be used. He also noted that, while there was some favourable toxicological response to the XXXXXXXX formulation, the lack of human data remained a severe impediment to changing the current scheduling arrangements. However he believed that the data did support an argument that the XXXXXXXX formulation was safer than the XXXXXXXX product.

The XXXXXXXX Representative indicated that there was a need to have a range of herbicides in the marketplace to minimise the resistance that was occurring with glyphosate. However, in light of the fact that there was no antidote to poisoning and that paraquat was available, albeit in Schedule 7 with restrictions, XXXXXXXX was not supportive of a change in scheduling until there was better human data.

OUTCOME

The Committee considered that its concerns relating to the lack of toxicological evidence to support a Schedule 6 classification had not been sufficiently overcome to amend the scheduling of paraquat at this time. Accordingly, the Committee agreed that, based on the unique toxicity profile of paraquat, including its capacity to cause mortality, that paraquat continue to be included in Schedule 7 of the SUSDP.

[Paragraphs deleted**]**

4.2 ALKALINE SALTS

PURPOSE

The Committee considered the scheduling of alkaline salts with regards to use in dishwasher products.

BACKGROUND

The February 2004 NDPSC Meeting considered a review of alkaline salts by XXXXXXXX. The review addressed issues including the cut-off pH for scheduling, total alkalinity, the concentration at which the pH of a product should be measured, and the greater accessibility of dishwasher detergents compared with laundry detergents in the home. Among the review's proposals was changing the cut-off pH for inclusion in Schedule 5 to "more than 11.0". Members generally agreed that there was insufficient information to consider amending the Schedule 5 entry for alkaline salts.

At the June 2004 NDPSC Meeting the Committee noted a XXXXXXXX review of the international regulation of alkaline salts. Members were of the view that to reduce the pH cut-off for alkaline salts in Schedule 5 to pH 11 the Committee would need to know the number of products currently marketed with a pH between 11 and 11.5 and the number of harmful exposures attributed to the use of these products.

At the October 2004 and June 2005 NDPSC Meeting, the Committee considered data from various Poison Information Centres (PICs) concerning alkaline salt exposures. The Committee agreed that while this data was useful, there was still a lack of outcome data and thus insufficient information to justify a change in the scheduling of alkaline salts.

At the October 2005 NDPSC Meeting the Committee considered further data on the products listed in the PIC reports. It was agreed that all current Schedule 5 dishwashing products containing alkaline salts (i.e. with a pH > 11.5) were to have a child resistant closure (CRC) to reduce any potential for harm. The Committee further agreed to include a new entry in Part 1 Interpretation to explicitly identify powders as solids. In addition, Members agreed to a slight editorial change to the alkaline salts entry under Part 2, 25 (1) to clarify that a 5 kilogram capacity may substitute for the existing 5 litre capacity where appropriate.

The October 2005 NDPSC Meeting also agreed that:

- There was insufficient information to justify a scheduling change at this time through reducing the pH cut-off for alkaline salts in Schedule 5 from a pH of 11.5 to 11.
- There was sufficient data linking the high pH (>12.5) alkaline salt dishwasher products to a number of severe injuries to children to warrant foreshadowing of consideration of a scheduling change for these products to a more restrictive schedule at the February 2006 NDPSC Meeting, including the possibility of removing these products from the domestic market completely.
- A more restrictive schedule would reduce harm and encourage the ongoing industry move to lower pH formulations.
- Foreshadowing was appropriate because of concerns about possible impact on important commercial use and that there appeared to be no current issues arising from products for commercial business use. This proposal would also affect at least two current domestic products. Foreshadowing would therefore allow time for additional consultation.

DISCUSSION

The Committee recalled the following points from submissions to the October 2005 NDPSC Meeting:

- A submission from XXXXXXXX gave details of an incident involving a child accessing an alkaline salt dishwasher powder (XXXXXXXX, pH 13.5), noting that the child had accessed the dishwasher powder from a cupboard under the sink. This

child was able to remove the CRC and swallow a large mouthful of powder, sustaining severe injuries.

- XXXXXXXX asserted that dishwasher detergents are common household products and are frequently stored in readily accessible places. Many products on the market are highly caustic. A review of the XXXXXXXX data revealed that in the last 6 years, 96 children under 4 years of age presented following ingestion of dishwasher detergent. Roughly one third of these children required admission for endoscopy and treatment following the ingestion.
- XXXXXXXX also asserted that both the acute and long term sequelae of caustic burns due to ingestion of dishwasher detergent could be minimised by reducing the pH of products on the market. Even a functional CRC was no guarantee that a child will not be able to access the contents. XXXXXXXX had requested that consideration be given by the Committee as to a safe upper limit for pH of caustic dishwasher detergents.
- A submission from XXXXXXXX also referred to the case study discussed above. The submission detailed the progress of the child following the incident including operations and the ongoing requirement for gastrostomy feeding, a situation which may possibly be long term. XXXXXXXX.
- XXXXXXXX asserted that caustic oesophageal burns are a cause of severe morbidity in children that experience them and CRCs for very high pH products are not sufficient to prevent an incident such as happened to the toddler. XXXXXXXX recommended that the Committee consider a restriction of the pH for dishwashing powders to minimise the chance of a severe oesophageal burn.
- A submission from XXXXXXXX in New Zealand highlighted a cluster of severe injuries from ingestion of dishwasher powder in young children (5 within a period of 4 months: XXXXXXXX).
- A submission from XXXXXXXX, in response to the Committee's request that XXXXXXXX approach the manufacturers of dishwasher detergents seeking information on the pH strengths and market share of their products, included:
    - Data on the dishwasher detergent market which indicated that XXXXXXXX had the largest market share for all formulations, with XXXXXXXX of liquids, XXXXXXXX of powders and XXXXXXXX of the tablets. The other major players were XXXXXXXX.
    - Dishwasher detergent brand data was supplied for the key products that represent more than 90% of the sales in Australia. The data included poisons schedule, pH, presence of a CRC, recent changes to packaging and market share.
    - This data showed the pH of XXXXXXXX and XXXXXXXX were 13.6 and 13-14 respectively.
- With regard to a coordinated response from industry about extra steps to reduce alkaline salt poisonings, XXXXXXXX advised that the vast majority of dishwasher

products are used safely and effectively as intended. Additionally, two major brands have implemented product packaging changes for individual product lines in 2005 to assist in reducing exposures (XXXXXXXX). XXXXXXXX asserted that there were some consumer behaviours and other factors that may increase the risk of adverse exposures including:

  - Inappropriate storage, including easy access by children or with the CRC not engaged.
  - Older dishwashers or malfunctions that lead to sludge in machines post-wash.
  - Product being placed in machines before needed with the door left open.
- XXXXXXXX therefore considered that education and awareness are key issues and believed there was opportunity to work with KidSafe type programs to promote safe practices.

Additionally, at the October 2005 NDPSC Meeting a Member made the following points with regard to the issue of dishwasher detergents containing alkaline salts in New Zealand:

- There are basically two types of dishwasher products on the market:
  - older generation, higher pH, alkaline salt products; and
  - the newer, lower pH, enzyme/alkaline salt products.
- New Zealand had similar issues to Australia with regards to addressing alkaline salts poisonings. A Member informed the Committee the potential for poisonings may even be greater in New Zealand given the lower market penetration of the low pH enzyme based products **[**remainder of sentence deleted**]**. This probably reflects the relatively high level of local manufacture of the generic brands using the older (and cheaper), high pH formulations.
- All dishwasher detergents containing alkaline salts in New Zealand were still in the transitional part of the *Hazardous Substances and New Organisms Act* and as such are covered by the old toxic substances regulations which are largely in line with the Australian scheduling.

A Member advised that since the October 2005 NDPSC Meeting there had been a further 2 cases of children receiving significant injuries from alkaline salt dishwashing products in New Zealand.

The Committee considered a submission from XXXXXXXX making the following points:

- Confirmed that XXXXXXXX are manufacturers of automatic dishwasher powders with a pH > 12.5, and are fully committed to ensuring that, as a minimum quality standard, these products comply with all regulatory requirements and consumer safety standards.

- Confirmed that the products in question have previously been tested and complied with Australian regulatory requirements governing child resistant packaging. XXXXXXXX have further modified the packaging to improve its child resistant features XXXXXXXX.
- Regarding the foreshadowed change, the impact on products would be significant in that XXXXXXXX would be both commercially and competitively precluded from supplying the market with an auto dishwasher powder with a pH > 12.5. There would also be major changes to the labelling, packaging and presentation of these products as well as significant costs incurred to reformulate and carry out the necessary stability work. All existing stock would need to be managed out of the supply chain.
- Notwithstanding this XXXXXXXX had no objection to reformulating and therefore requested twelve months to fully comply from notification of the change, i.e. by 1 March 2007.

The Members also considered a submission from XXXXXXXX supporting the XXXXXXXX submission above i.e. supports a period to introduce changes to products. XXXXXXXX also contended that a Schedule 7 entry in this instance was unnecessary and XXXXXXXX had concerns that a Schedule 7 entry may have unintended consequences for industrial products i.e. when used in commercial kitchens.

[Section deleted**]**

The Committee also noted advice from a Member regarding the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) classification for corrosivity. With regard to skin and eye irritation/corrosion, a mixture is considered skin corrosive or eye corrosive if it has a pH of 2 or less, or a pH of 11.5 or greater.

A Member asserted that, while there were a large number of reports where children inappropriately accessed alkaline salts in dishwashing products, only a small percentage of these resulted in significant harm. The Committee generally agreed that it was only a minority of products, those with high pH (i.e. pH > 12.5, 2 products), that were associated with the small number of significant injuries. It was further noted that there was a big drop in pH from these high pH formulations to the remaining products which usually had pH strengths below 11.5. The Committee therefore agreed that high pH (>12.5) alkaline salt dishwashing products are to be removed from the domestic market.

The Committee also agreed, however, that high pH products have a place in industries such as commercial kitchens, restaurants and hospitality. A Member advised that the high pH dishwashing products were used for the speed that could be achieved when washing dishes (usually with machines and temperature settings different to domestic machines) which can be important in commercial situations.

A Schedule 7 listing to remove these high pH alkaline salt dishwashing products from the domestic market was initially considered by Members but was deemed to inappropriately impact on commercial use. The Committee instead agreed to remove these products from the domestic market by including domestic use of alkaline salts in dishwashing products

with pH > 12.5 in Appendix C as they are substances of such danger to health as to warrant prohibition of sale, supply and use. Additionally, while commercial use of these high pH dishwasher products did not pose the immediate danger to children that domestic use did, the Committee agreed that the inherent risk from exposure to this strength product justified placing such products into Schedule 6. However, as packaging requirements for industrial use are set by the Australian Safety and Compensation Council, and as the Schedule 6 entry would not include products for domestic use, the Committee agreed that the was no need to mandate a CRC for products captured by the Schedule 6 entry.

The Committee also considered the request in both submissions for an extended implementation period for any restrictive scheduling of the high pH domestic products. Members agreed, however, that as there was sufficient public health and safety concern to put these products into Appendix C it would be inappropriate to allow these products to be on the market beyond 1 September 2006, the standard implementation date for decisions from this Meeting.

DECISION 2006/46 - 11

The Committee agreed that, based on a number of severe injuries to children linked to high pH (>12.5) alkaline salt dishwasher products, all such products are to be removed from the domestic market through inclusion in Appendix C. Additionally, the Committee agreed that such products (pH>12.5) for non-domestic use are to be included in Schedule 6 as they have a moderate potential for causing harm because of their corrosive properties.

Schedule 5 – Amendment

† ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination:

(a) in solid orthodontic device cleaning preparations, the pH of which as an “in-use” aqueous solution is more than 11.5;

(b) in solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 11.5 but less than or equal to 12.5;

(c) in other solid preparations, the pH of which in a 10 g/L aqueous solution is more than 11.5; or

(d) in liquid or semi-solid preparations the pH of which is more than 11.5,

except when separately specified in these schedules.

Schedule 6 – New Entry

† ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for non-domestic use:

(a) in solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 12.5; or

(b) in liquid or semi-solid automatic dishwashing preparations the pH of which is more than 12.5.

Appendix C – New Entry

ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for domestic use:

(a) in solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 12.5; or

(b) in liquid or semi-solid automatic dishwashing preparations the pH of which is more than 12.5.

4.2.1 LYE WATER

PURPOSE

The Committee considered the scheduling of the various possible alkaline substances in lye water including the packaging requirements for lye water products.

BACKGROUND

A detailed background to the scheduling of alkaline salts is set out under item 4.2.

Lye water can refer to either sodium hydroxide, potassium hydroxide or a mixture of both in aqueous solution. However, lye water can also refer to sodium or potassium carbonate solutions. It is used in the traditional manufacture of soap and as a cleaning agent. Lye water is also an ingredient in Asian cooking where it is usually added in small amounts (table spoon volumes) to bind ingredients such as rice.

At the June 2005 NDPSC Meeting the XXXXXXXX Member advised that analysis of a cooking condiment marketed as “Lye Water” was undertaken following the hospitalisation of a child with severe burns to the oesophagus and stomach. The product

in question was manufactured by XXXXXXXX in Hong Kong and has been imported into Australia by a number of distributors. As a result of this, discussions were held with XXXXXXXX with a view to having this product recalled from the domestic market as quickly as possible.

The XXXXXXXX Member also asserted that the regulatory areas dealing with food in some other jurisdictions had chosen not to initiate recall action in relation to this product.

DISCUSSION

The Committee considered a submission from XXXXXXXX requesting amendments to the alkaline salts entries in the SUSDP to deal with concerns over the safety of lye water. The Committee particularly noted the following:

- Three incidents of poisonings have been reported from ingestion of lye water (the products were used as an ingredient in Asian cooking).
- XXXXXXXX had concerns surrounding the packaging of lye water products and the ease with which they can be accessed by infants and children.

XXXXXXXX recommended:

- That the Schedule 5 entry for alkaline salts be amended to ensure the packaging requirements include the compulsory addition of a child resistant closure (CRC). Specifically, they are recommending that this apply to:
    - Containers of 500 mL or less;
    - Where captured by the Schedule 5 alkaline salts entry, part (d) “in liquid or semi-solid preparations the pH of which is more than 11.5”;
    - Products sold for use as food additives; and
    - Retail products intended for use in the home.
- The requirement would not need to apply to products for commercial use.

Members also were advised that XXXXXXXX had provided details of the lye water product referred to by the XXXXXXXX Member at the June 2005 NDPSC Meeting. An analysis of the product determined:

- The product contained 48.8% (w/w) potassium carbonate and 2.5% (w/w) sodium carbonate with a pH of ~14.
- The combined potassium and sodium carbonate content represents a total alkalinity equivalent to ~47% (w/v) of sodium hydroxide.
- The labelling included, in small lettering, a “CAUTION”, “FIRST AID” and “SAFETY DIRECTIONS”.
- It states, again in very small lettering, that “This product is NOT a beverage”. However, “NUTRITION INFORMATION” is given. The analyst was of the opinion

that to display a "NUTRITION INFORMATION" panel on this product was dangerously misleading as to its nature, in spite of its easily-missed disclaimer that it was not a beverage.

The XXXXXXXX Member advised that XXXXXXXX considered the above product to be an unlabelled, and therefore non-compliant, Schedule 5 product.

The Committee also considered:

- A fact sheet on lye water released by the SA Department of Health.
- A NSW Food Authority Media Release of 21 July 2005 warning that care is required when handling lye water.
- Brief details of a Food Standards Australia New Zealand recall of a lye water product (XXXXXXXX).

The Committee noted that:

- where sodium or potassium hydroxide are part of a lye water formulation the product would be required to be fitted with a CRC, as set out under Part 1, paragraph 25(1) of the SUSDP, regardless of the pH of the product. Additionally, if the pH of the liquid was more than 11.5 it would also be captured by either the Schedule 5 or 6 entries for sodium or potassium hydroxide, depending on concentration.
- where lye water has been made from alkaline salts such as sodium or potassium carbonate, with no sodium or potassium hydroxide, then it would be captured by the Schedule 5 alkaline salts entry if it had a pH greater than 11.5, with associated labelling requirements. However, there would be no requirement for a CRC.

A Member questioned whether lye water would fall under the general exemption for food in Appendix A. The Committee agreed, however, that lye water was a food additive and therefore did not qualify for the Appendix A general exemption. Another Member suggested that perhaps manufacturers did not realise that lye water would be captured by either the alkaline salts entry or the sodium or potassium hydroxide entries. The Committee agreed to the Members suggestion to include a cross reference in the SUSDP index linking lye water to the appropriate schedule entries.

A Member proposed that perhaps a Schedule 6 entry for alkaline salt food additives with a pH > 12.5 would be appropriate given that lye water appears to have a pH of about 14 and would have a least some propensity for use in domestic kitchens. Another Member noted that the lye water situation, where the product was unlabelled, without CRC's, and often presented as a food in inappropriate packaging (i.e. a bottle resembling a clear wine bottle), is somewhat different to the alkaline salt dishwashing product situation considered in item 4.2. The Member asserted that the alkaline salt dishwashing products were labelled, largely compliant, and that continued injuries in light of this situation required the further restrictions outlined in item 4.2.

The Members agreed that the intent was not to eliminate the use of lye water, rather, the intent was to minimise any safety risk by having appropriate safeguards in place. The Committee agreed that the first step in controlling the lye water risk was to introduce a mandatory CRC. Members also agreed that the current failure to comply with the Schedule 5 labelling requirements was an enforcement issue. Members generally agreed that further restrictions, such as a Schedule 6 entry, may need to be considered at a future date should the problem fail to resolve.

The Committee also considered XXXXXXXX request that the volume limit for mandating CRC's be 500 mL. A Member advised that this request had been discussed at the recent XXXXXXXX where it was noted that although current lye water products appeared to all be in 500 mL bottles, if a larger bottle was brought to market (i.e. 2 L), this could still find use in a domestic setting. Members agreed that a volume limit of 2.5 litres or less was appropriate to minimise risk posed by lye water products to children.

OUTCOME

The Committee agreed to foreshadow an amendment to Part 1, Paragraph 25(1) of the SUSDP so that food additives captured by the alkaline salts entries (i.e. lye water with a pH > 11.5) are to be required to have a child resistant closure where the volume is 2.5 litres or less as these products have the potential to cause harm if inappropriately accessed by a child.

FORESHADOWED DECISION (for consideration at the June 2006 Meeting)

Part 2 – Labels and Containers

Child-resistant closures – Amendment

Paragraph 25(1) **–** Amend entry by inserting the following table entry relating to alkaline salts:

25. (1) If a poison listed in column 1 of the following table is sold or supplied in a container having a nominal capacity specified for that poison in column 2 it must be closed with a child-resistant closure.

TABLE

Column 1 **Name of the poison**	**Column 2** **Nominal Capacity**
Alkaline salts included in Schedule 5, when packed and labelled as a food additive.	2.5 litres or less

4.3 CHLORHEXIDINE

PURPOSE

The Committee considered the inclusion of chlorhexidine in Schedule 7 of the SUSDP.

BACKGROUND

At NDPSC (45), the Committee received the OCS report which noted that the inhalational LC_{50} for chlorhexidine acetate of 300 mg/m^3 was consistent with a Schedule 7 classification. The OCS evaluation also concluded that, on the basis of inhalational toxicity alone, 10% chlorhexidine would be an appropriate cut-off from Schedule 7 to Schedule 5 as the NDPSC guidelines indicate that an LC_{50} of >3000 mg/m^3 is consistent with Schedule 5.

However, the OCS report also noted that, according to the available information that has predictive value with respect to possible adverse effects arising from accidental ocular exposure to chlorhexidine, a concentration of 2 % chlorhexidine gluconate, equivalent to approximately 1.2 % chlorhexidine base, is sufficiently irritant to warrant inclusion in Schedule 5 of the SUSDP. Below this concentration, scheduling was not considered necessary. However, due to the paucity of data for intermediate concentrations of chlorhexidine, setting a cut-off from Schedule 5 to higher schedules was problematic. Chlorhexidine gluconate was likely to produce reversible eye injury at 4%, but effects were irreversible at 20%. Without specific data for intermediate concentrations, the maximum concentration of chlorhexidine that could be supported for inclusion in Schedule 5 was the equivalent of 4% chlorhexidine gluconate (i.e. 2.3 % of the chlorhexidine base), with higher concentrations to be included in Schedule 7.

The OCS evaluation therefore recommended that the Committee consider 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 OCS also suggested that the Committee may also wish to consider the long history of chlorhexidine use in hospitals as a surgical scrub, for pre-operative skin disinfection and for the disinfection of inanimate objects, as well as in other antiseptic products. Given the toxicology concerns outlined in the OCS evaluation report the Committee considered broadening the OCS recommendation from animal use to all uses.

It was noted that a search of the Australian Registry of Therapeutic Goods (ARTG) revealed 97 products containing chlorhexidine at a variety of strengths. The ARTG entries were summarised in the following table:

ARTG entries for 97 products containing chlorhexidine and OCS proposed scheduling				
Unknown	≤ 1% (exempt)	≤ 2.5% (S5)	3% (S7)	> 3% (S7)
31	40	19	6	1 (11%)

The Committee also noted that chlorhexidine was not listed in the *Required Advisory Statements for Medicine Labels* (RASML). The Committee considered referring the issue of labelling of chlorhexidine for human use to the OTC Medicines Evaluation Section.

The Committee further 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 as set out above) 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 Committee therefore considered a 3% exemption to Schedule 5 to minimise regulatory impact.

The Committee noted a submission received from XXXXXXXX which opposed any changes to the Appendix B status of chlorhexidine, from the XXXXXXXX which expressed concern over the possibility of chlorhexidine and its derivatives being scheduled and covered by a general entry rather than a specific pesticide and veterinary medicine entry and from XXXXXXXX which noted that chlorhexidine had wide application in a number of sectors – oral hygiene, therapeutic products, cleaning products etc. and therefore any scheduling outcomes may have specific product impacts. XXXXXXXX and XXXXXXXX indicated an interest in chlorhexidine, noting a long history of supply of chlorhexidine for oral care.

Concerns were raised by the XXXXXXXX about the scheduling of chlorhexidine with respect to the possible considerable impact on the large number of existing registered products. The XXXXXXXX Member suggested that the Committee consider foreshadowing a decision to allow consultation with industry, in particular the dairy industry.

Accordingly, the October 2005 meeting agreed to foreshadow the inclusion of chlorhexidine in Schedule 7 on the basis of severe eye irritancy. The Committee also agreed that the toxicology data justified an exception to Schedule 5 for 3 percent or less and an exemption to unscheduled for 1 percent or less. The Committee agreed that there were insufficient data to justify a Schedule 6 exception.

The Committee requested the APVMA representative to provide details of all registered products containing chlorhexidine.

The Secretariat was asked to gazette the proposals to allow for wide consultation and to encourage submission of information that would support further cut-off levels. The Secretariat was also asked to obtain any ADRAC reports involving chlorhexidine.

DISCUSSION

At the February meeting, Public submissions were received from XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX.

XXXXXXXX noted that:

- The use of chlorhexidine and iodophores are significant components of ensuring good udder health and have figured prominently as part of the programme, including appropriate use. The two veterinarians who have managed Countdown Downunder since its inception have reported that in all the training courses conducted and meetings they have attended with respect to Countdown Downunder they have never heard anyone make a mention of eye irritation as being an issue with the use of chlorhexidine either in its application concentration or in concentrate form prior to being prepared on farm. XXXXXXXX would be interested in understanding the problem in this regard given that the major use of chlorhexidine in the dairy industry is as an udder disinfectant and the issue of eye irritation does not, at least anecdotally, appear to be a problem.
- The dairy industry has well developed on-farm haccp-based food safety and quality assurance programmes. All dairy farmers in Australia have operated on one of these company-based systems for several years. They require, amongst other things, appropriate competency in the storage and management of agricultural and veterinary chemicals. These programmes are independently audited and monitored by State food authorities. Therefore, dairy farmers are able to demonstrate appropriate use of products such as chlorhexidine as part of their daily work practices.
- With respect to the specifics of the issue, the dairy industry is strongly opposed to the scheduling proposal on the grounds that:

  - the concentrated form of chlorhexidine based veterinary chemicals, if made S7 products, would require dairy farmers in several jurisdictions, including Victoria (where 66% of dairy farmer operate), to obtain a permit from the relevant authority to obtain and use these products. The on-farm food safety programmes have demonstrated effective use, through audit, without the need for a licence and a licence should not be required in the future to purchase such a product.

  - the scheduling requirement would add unnecessary cost and regulatory burden on dairy farmers. This regulatory burden would be added in a situation where there has been widespread use of the product for many years without adverse outcomes.

  - any desired occupational health and safety outcome could be readily achieved by amending product labels to include a statement regarding personal protective equipment, in particular eye protection when handling and mixing the concentrated products.

XXXXXXXX

The XXXXXXXX noted that there was an inconsistency in placing chlorhexidine in Schedule 7 when compared with other substances such as sodium hydroxide which may cause ocular and tissue damage but which are included in Schedule 6.

XXXXXXXX

XXXXXXXX noted that there were a number of agvet products, with long history of use, that contained more than 3% chlorhexidine yet XXXXXXXX was not aware that there was significant adverse human experience with the use of such products.

XXXXXXXX also noted that current products containing greater than 3% chlorhexidine will be effectively removed from the market through the imposition of the foreshadowed decision. Concern was also expressed that the foreshadowed Schedule 7 entry may have unintended consequences for "industrial products" through the flow-on effects of sale/supply and use controls such as licensing requirements of some State jurisdictions.

XXXXXXXX

XXXXXXXX raised two questions, the first of which was directed to NDPSC.

- what "constraints" do they (NDPSC?) propose to place on the supply and use of chlorhexidine-containing products when they present as Schedule 7 preparations, given that as S7 substances, "special regulations" can be applied to restrict availability, possession, storage or use? (**Secretary's note**: This would seem to be a matter for State authorities who have responsibility for supply and use of veterinary medicines)
- Regarding supply as S5, Caution - substances where the potential to cause harm is to be reduced through appropriate packaging with simple warnings and safety directions on the labels. XXXXXXXX wonders what might be considered as "appropriate packaging" and who makes that decision - OCS, APVMA? (**Secretary's note**: This is a matter for the APVMA, possibly in consultation with the Office of the Australian Safety and Compensation Council (formerly NOHSC), and the OCS.)

Advice from ADRAC

The Committee also received advice from ADRAC. ADRAC advised that, following a consumer complaint to the Minister for Health and Ageing in relation to an allergic reaction to XXXXXXXX and that the label contained no information about the possibility of an allergic reaction, the ADRAC requested in September 2005 that a review be conducted of reports of adverse reactions associated with chlorhexidine, including XXXXXXXX mouth wash. The Committee also thought it may be appropriate to publish a Bulletin article on this topic, possibly after the review was completed. As a result, ADRAC has been able to provide the NDPSC with the following detailed analysis.

Identification of products

The ARTG was searched for products that contained chlorhexidine, chlorhexidine acetate, chlorhexidine gluconate or chlorhexidine hydrochloride. Both current and cancelled registrations and listings were searched. A total of 296 products were identified. The ADRAC database dictionary was then searched to identify products that were on that ARTG list. This approach was necessary because many products containing chlorhexidine are multi-ingredient preparations. A total of 41 entries were identified. It should be noted that some of these entries were unclear with respect to which product on the ARTG they referred to, in that concentration or formulation was not always specified. A list of the products identified from the ADRAC dictionary is available.

The following additional entries were unclear as to whether they referred to a product containing chlorhexidine and the reports were reviewed manually: XXXXXXXX, XXXXXXXX and XXXXXXXX. If, on review it was clear the report referred to a product containing chlorhexidine then that report was added to the total.

Reports

The database contained 249 reports that included products containing chlorhexidine. The product containing chlorhexidine was the sole suspected drug in 190 of these reports. 24 reports concerned serious ADRs and in 14 of these reports a product containing chlorhexidine was the sole suspected drug. This determination was made using the outcome of death and the severity indicators of life-threatening, hospitalised or prolonged hospitalisation. The database does not allow further more detailed determination of serious ADR reports prior to mid 2005.

Deaths

One death was reported. **[**Section deleted**]**

Serious ADRs

18 serious reports included at least one of the terms in the allergy search listed below.

[Section deleted**]**

Topical reactions

On initial review it was apparent that the most frequently reported events related to topical reactions and to allergic reactions. The reports were then searched for groups of terms consistent with topical reactions. MedDRA preferred terms identified included: application site reaction, dermatitis, pruritus and rash (descriptor). There were 137 (53.9%) reports that contained at least one of these terms. In 3 (1.2%) reports the reaction was serious and the product containing chlorhexidine was the sole suspected drug. **[**Section deleted**]**

All 3 of these serious events where the chlorhexidine product was the sole suspected drug suggest that allergy was the cause of the reactions.

Allergic Reactions

MedDRA preferred terms that included the following words associated with allergy were included in a search for reports indicating allergic response: anaphylactic, anaphylactoid, angioneurotic oedema, bronchospasm, dyspnoea, hypersensitivity, hypotension, oedema, oedema (face, laryngeal, mouth, periorbital, tongue), shock, swelling face and urticaria. There were 77 (30.3%) of these reports and in 12 reports (4.7%) of serious reactions concerning allergy a product containing chlorhexidine was the sole suspected drug.

Ototoxicity

There were 22 reports of ototoxicity or deafness. 20 of these reports were submitted by an unknown General Practitioner in June 1973. The reporter indicated that he was personally aware of about 20 cases of ototoxicity when chlorhexidine was used as an antiseptic skin preparation prior to surgery to repair perforation of the tympanic membrane. He noted that this was associated with permanent, irreversible gross perceptive hearing loss. No individual patient was identified in these reports and no audiograms were submitted.

The two other reports were of deafness. **[**Section deleted**]**

ADRAC Analysis

Allergic reactions are of most concern for products containing chlorhexidine. From the above data it is clear that these products can very occasionally be associated with severe, even life-threatening adverse events.

Outcome from ADRAC consideration

The 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. It was noted that products such as XXXXXXXX contain benzydamide in addition to chlorhexidine, and that benzydamide is also know to cause allergic reactions. Members commented on the lack of evidence showing that chlorhexidine was an effective decontaminant and suggested that its use may be limited.

The Committee noted that chlorhexidine products had been in widespread use for considerable time without apparent problems in respect to eye irritancy, particularly in agricultural use. However the ADRAC reports were of concern.

A member advised that the products with a high level of chlorhexidine were solid dose formulations such as pessaries (1g/pessary) while the next highest concentrations (6.7% chlorhexidine) were dental sprays for cats and dogs. The XXXXXXXX representative also reported that the APVMA had not received any adverse experience reports in humans or animals involving eye irritancy although there had been some reports of allergic reactions in dogs. The importance of the ‘Countdown Downunder’ Program for

mastitis control, including its public health significance, required the continued availability of chlorhexidine to dairy farmers.

A member also noted that the Committees 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 the Committee should schedule 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. It was also important that there be consistency in approach with caustic substances which were included in Schedule 6.

An exemption for solid dose preparations was granted on the basis that these formulations would not present an eye irritancy hazard to the user.

DECISION 2006/46 - 12

On the basis of the potential for severe eye irritancy, the Committee agreed 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.

Schedule 7 - New entry

CHLORHEXIDINE **except**:

(a) when included in Schedule 5 or 6;

(b) in preparations containing 1 per cent or less of chlorhexidine, or

(c) when in solid preparations.

Schedule 6 – New Entry

CHLORHEXIDINE in preparations containing 7 per cent or less of chlorhexidine **except**:

(a) when included in Schedule 5;

(b) in preparations containing 1 per cent or less of chlorhexidine; or

(c) when in solid preparations.

Schedule 5 – New entry

CHLORHEXIDINE in preparations containing 3 per cent or less of chlorhexidine **except**:

(a) in preparations containing 1 per cent or less of chlorhexidine; or

(b) when in solid preparations.

Appendix B – Amendment

CHLORHEXIDINE – delete entry.

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

5.1 SUSDP, PART 4

5.1.1 CYSTEAMINE HYDROCHLORIDE

PURPOSE

The Committee considered the scheduling of cysteamine hydrochloride.

BACKGROUND

Cysteamine hydrochloride is a salt derivative of cysteamine. Cysteamine has been used therapeutically for the management of nephropathic cystinosis in children and adults. Cystinosis is an inherited defect of lysosome transport of cystine. Cysteamine hydrochloride has also been used as an ingredient in cosmetic products as a hair-waving and straightening agent, and as a reducing agent.

At the August 1997 NDPSC Meeting the Committee agreed to include cysteamine in Schedule 4. The Members noted that the PI identified somnolence as an adverse effect and therefore also agreed to an Appendix K entry for cysteamine.

The conversion ratio from cysteamine hydrochloride to freebase cysteamine is ~1.47:1. Thus 7.5% cysteamine hydrochloride is ~5.1% cysteamine. 6% cysteamine would be equivalent to 8.8% cysteamine hydrochloride.

DISCUSSION

The Committee considered a submission XXXXXXXX requesting an exemption to the cysteamine Schedule 4 entry for topical cosmetic use.

The Members noted that XXXXXXXX wished to introduce cysteamine hydrochloride as a replacement for XXXXXXXX in a XXXXXXXX. **[**Sentence deleted**]** The pH of the product formulations ranges from approximately 11.7 to 12.4. It was asserted that currently XXXXXXXX products containing XXXXXXXX have a higher pH (approximately 12.6 to 13.2).

The Committee considered a XXXXXXXX evaluation of the XXXXXXXX submission. The evaluation report particularly noted:

- **[**Paragraph deleted**]**
- There have been a number of adverse reactions from therapeutic use of cysteamine.
- According to the MIMS Annual 2005, the most common adverse reactions from the therapeutic use of XXXXXXXX containing cysteamine bitartrate (50 or 150 mg) were vomiting, anorexia, fever, diarrhoea, lethargy and rash.
- Adverse reactions involving the gastrointestinal and central nervous systems were especially prominent at the initiation of cysteamine therapy. Central nervous system symptoms included seizures, lethargy, somnolence, depression, and encephalopathy. Gastrointestinal tract symptoms included nausea, vomiting, anorexia, and abdominal pain, sometimes severe. In addition, gastrointestinal ulceration and bleeding had been reported in patients on cysteamine bitartrate therapy.
- A cysteamine dose of 1.95 g/m^2/day (approximately 80 to 90 mg/kg/day) was associated with an increased number of withdrawals from treatment due to intolerance and an increased incidence of adverse effects (vomiting, lethargy, fever).
- Post-marketing reports included one report of interstitial nephritis with early renal failure. A causal relationship between this event and cysteamine bitartrate therapy has not been established. Cysteamine had occasionally been associated with reversible leucopenia and abnormal liver function studies.
- Dermal exposure would be the sole route of human exposure to XXXXXXXX. It was anticipated that the primary consumer would be women, who may use the product on XXXXXXXX. However, male consumers may also use the product to XXXXXXXX.
- Estimated dermal exposures from use of XXXXXXXX cysteamine formulations (10 minutes per event once every two weeks) was provided. The maximum systemic exposure per day was 0.12 mg/kg/day based on the estimated dermal exposure.
- Oral exposure would occur only in the event of accidental ingestion. If a 20 kg child ingested one teaspoon (~5-10 g) of a product containing XXXXXXXX cysteamine exposure would be 37.5 mg/kg. This exposure was roughly equivalent to the daily doses given for the treatment of nephropathic cystinosis, 30 to 75 mg/kg/day. The product package warning advised the consumer to keep product out of reach of children.

- Ocular exposure would only occur with accidental contact with eyes. The XXXXXXXX formulations containing cysteamine have high pH, and irritant properties are predicted. The product package warning advises the consumer to avoid contact with the eyes.

The Committee particularly noted the following points from the evaluation report's assessment of the toxicity information supplied in the submission:

- Cysteamine had low acute oral toxicity (LD_{50} 1352 mg/kg in mice). There was no dermal toxicity data.
- Cysteamine hydrochloride up to 7.5% (approximately 5.11% cysteamine) caused mild skin irritation. **[**Section deleted**]**
- Cysteamine hydrochloride showed no evidence of sensitisation XXXXXXXX concentrations of 7.5% and 5% in human patch tests. However, there was a single case report of cysteamine hydrochloride allergic contact dermatitis in a hairdresser. Cysteamine has been used as a reducing agent, typically at concentrations between 5% and 12%, in permanent wave solutions introduced to American beauty salons since 1993.
- At concentrations between 1-10%, cysteamine had caused serious damage to eyes (Members noted advice from the Secretariat that in this instance by "serious" the evaluator meant in the moderate to severe range as per the NDPSC guidelines). Details of the eye toxicity included:
    - **[**Section deleted**]** Out of ten eyes receiving 10% eye drops, five showed mild to moderate hyperaemia and thickening of the lower and upper eyelids after 10 days, leading to cessation of this treatment regimen. The eyes receiving 5%, 2% or 1% cysteamine eye drops showed no clinical signs of toxicity, but exhibited a dose dependent infiltration upon histopathological examination. The eyes treated with 0.5% or 0.1% cysteamine showed no clinical or histopathological signs of toxicity. Also, there were no adverse side effects reported in 29 patients exposed to 0.1% and 0.5% cysteamine eye drop in a clinical trial for up to 34 months.
- No robust repeated dose or long term studies in animals with cysteamine were identified.
- In the developmental and reproductive toxicity studies submitted, cysteamine at an oral dose of 375 mg/kg/day (1.5 times the maximum recommended human oral dose, based on body surface area) reduced the fertility of adult rats. The NOAEL for maternal toxicity was 100 mg/kg/day. In another study, the NOAEL for developmental effects was 75 mg/kg/day.
- The genotoxicity profile of cysteamine in vitro was mixed, but it was concluded to be negative in a well conducted in vivo micronucleus study in the mouse bone marrow. Cysteamine had not been tested for carcinogenic potential in long-term animal studies.

The Committee considered the following conclusions from the evaluation report:

- Wide dispersive use with intermittent dermal contact and possibly accidental ocular contact or oral ingestion of cysteamine was expected to occur among public consumers.
- The total daily systemic exposure of an individual was estimated to be 0.12 mg/kg bw/day (based on estimated dermal exposure for a 70 kg person) when used in the proposed XXXXXXXX products at concentrations up to XXXXXXXX cysteamine hydrochloride, or 37.5 mg/kg in the event of accidental ingestion. A cysteamine dose of 1.95 g/m^2/day (approximately 80 to 90 mg/kg/day) had been associated with an increased number of withdrawals from therapeutic treatment of nephropathic cystinosis due to intolerance and an increased incidence of adverse events. In addition, the NOAEL for cysteamine from the reproductive and developmental studies was 75 mg/kg/day. The margin of exposure to cysteamine was therefore estimated to be 625 or 313 under normal use, and in the event of accidental ingestion, respectively. Hence, the risk to the public was likely to be low.

The evaluation report supported the revision of the scheduling for use of cysteamine in topical cosmetic preparations containing 7.5% or less of cysteamine hydrochloride with provision of appropriate warning statements and/or safety directions on the label to reflect its eye irritation and skin sensitising potential. The evaluation report, however, did not recommend a specific schedule for cysteamine hydrochloride when used in cosmetics at a concentration of 7.5% or less. The Members were advised that subsequent discussion with the evaluator by the Secretariat established that the evaluator thought that cysteamine for cosmetic use at these concentrations lay on the border between Schedule 5 and 6 due to the eye irritancy.

The Committee were advised that a pre-meeting comment by XXXXXXXX on the evaluation report provided a reference for the oral LD_{50} study in mice.

The Members also noted that the Martindale Monograph for mercaptamine (the INN for cysteamine hydrochloride), in reference to therapeutic use, which indicated that it may cause gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhoea, and abdominal pain; rarely there may be gastrointestinal ulceration or bleeding. Other adverse effects included drowsiness, malaise, rashes, fever, flushing, and ventricular tachycardia. Mercaptamine may cause increases in liver enzyme values and precipitate hepatic coma in patients with overt hepatic damage. Interstitial nephritis has also occurred rarely. Nervousness, depression, and, rarely, hallucinations, have been reported.

A Member questioned whether there was a need for a warning statement against cosmetic use of cysteamine while pregnant given some evidence of developmental toxicity identified in the evaluation report. The Committee agreed that such a statement was not necessary as the worst-case scenario for female exposure had a safety factor between the estimated exposure and the No Observable Effect Level for developmental toxicity of 94 fold.

Additionally, the Committee decided that there was a need to include safety and first aid directions when for cosmetic use to reflect the eye irritancy potential. However,

Members considered that there was no need to include any such statements for sensitisation as the only concern was a single report of cysteamine induced allergic contact dermatitis in a hairdresser, and the evaluation report had noted no evidence of sensitisation in human patch tests.

Members further noted a submission from XXXXXXXX registering an interest in cysteamine hydrochloride.

DECISION 2006/46 - 13

The Committee agreed:

- That cysteamine hydrochloride for cosmetic use does not warrant capture by Schedule 4 which is for therapeutic use.
- That a new entry in Schedule 6 be included for greater than 6% cysteamine for cosmetic use (equivalent to 8.8% cysteamine hydrochloride) because of severe eye irritancy potential.
- That a new entry in Schedule 5 be include for less than or equal to 6% cysteamine for cosmetic use because of a slight to moderate eye irritancy potential.
- That 1% or less of cysteamine for cosmetic use be exempt from the requirements of scheduling as it presents a very low toxicity or eye irritancy risk.
- To include in the SUSDP the first aid instruction “If in eyes wash out with water” and the safety direction “Avoid contact with eyes” due to the Committee’s particular concerns around the eye irritancy potential.

Schedule 4 – Amendment

CYSTEAMINE – amend entry to read:

CYSTEAMINE for human therapeutic use.

Schedule 5 – New entry

CYSTEAMINE in cosmetic preparations containing 6 per cent or less of cysteamine
except in preparations containing 1 per cent or less of cysteamine.

Schedule 6 – New entry

CYSTEAMINE for cosmetic use **except**:

(a) when included in Schedule 5; or

(b) in preparations containing 1 per cent or less of cysteamine.

Appendix E - Part 2 – New entry

POISON	**STANDARD STATEMENTS**
Cysteamine	E1

Appendix F - Part 3 – New Entry

Poison	**Warning Statement**	**Safety Directions**
Cysteamine		1

5.1.2 SODIUM POLYSTYRENE SULPHONATE

PURPOSE

The Committee considered the scheduling of sodium polystyrene sulphonate (SPS).

BACKGROUND

SPS is the sodium salt of polystyrene sulphonic acid (PSS). The SPS polymer is highly charged with anionic sulphonic acid groups linked to aromatic rings of the polymer backbone. SPS is available in two forms:

- A water-soluble non-cross linked form used as the cosmetic ingredient (trade name XXXXXXXX, an off-white powder consisting of 90% SPS with a molecular weight of approximately 130,000 where a 30% aqueous solution has a pH range of 5.5-8.5.). SPS is used in formulations overseas including hair care (such as hair styling aid, thermal protective products, shampoos and conditioners) and anti-wrinkle skin care products. SPS is also used as emulsion stabilisers, film formers, surfactants and viscosity controlling agents.
- A cross-linked water-insoluble form which is used in current therapeutic applications. SPS is currently the active used in a listed medicine for treatment of hyperkalemia and hyperphosphatemia according to the ARTG. The function of the SPS in this therapeutic product was to treat high blood level potassium by removing potassium from the body by exchanging it with sodium in the gut. SPS is also used as an excipient in four phentermine resin products. The therapeutic uses of SPS are substantially different from the cosmetic use.

At the August and November 1999 NDPSC Meetings the Committee agreed to include SPS in Schedule 4 to harmonise with New Zealand as recommended by the trans-Tasman Harmonisation Working Party.

At the June 2005 NDPSC Meeting the Members considered an application from XXXXXXXX requesting an exemption from Schedule 4 for topical cosmetic use of

sodium polystyrene sulphonate. The Committee agreed that, while the proposed uses were likely to pose a low hazard/risk and were probably either Schedule 5 or exempt, it was not possible using the submitted data to be definitive about a scheduling decision in terms of topical cosmetic use. The Committee agreed, in the absence of health and safety studies on the product, that the scheduling of sodium polystyrene sulphonate remained appropriate.

DISCUSSION

The Committee considered an additional submission from XXXXXXXX addressing the data deficiencies identified by the Committee at the June 2005 NDPSC Meeting, particularly the Committee's desire to see the full health and safety studies for Flexan II.

The Members noted that the XXXXXXXX evaluation of the additional XXXXXXXX submission included both a review of the additional data submitted by XXXXXXXX and the original XXXXXXXX submission. The Members recalled the following points from the original submission:

- XXXXXXXX wished to import a product branded XXXXXXXX which contains SPS at a level of XXXXXXXX.
    - XXXXXXXX claimed that there were a number of cosmetic benefits of SPS, particularly for **[**remainder of paragraph deleted**]**.
- It is hydrophilic and easily rinsed off.
- Cosmetic products using SPS were widely sold overseas and that XXXXXXXX was currently marketed in Europe and had been sold for over two years without any adverse reports. This product contained warning statements of – "Caution: Pressurised Container, Keep out of Reach of Children"; "Avoid Spraying near eyes"; and "Use only as directed".
- The US National Library of Medicine Household Products Database, which compiles information from product MSDS and labels, noted the use of SPS in 5 hair care products in the US. The percentages of SPS in the products was not stated. Information from National Starch and Chemical on 5 typical hair care product formulations containing SPS noted the chemical present at between 1.0 and 5.0%.

The Committee was advised that the additional XXXXXXXX submission included the following new information:

- Details of toxicology tests conducted on behalf of XXXXXXXX.
- A copy of a letter from XXXXXXXX to XXXXXXXX confirming that SPS was listed on Schedule F of the Canadian Food and Drugs Act and was acceptable for use in leave-on and rinse-off cosmetic products.

Members particularly noted the following from the evaluation report:

- Acute oral and dermal toxicity studies submitted for 30% SPS showed low toxicity (LD_{50} > 5 g/kg body weight).
- SPS appeared to be a skin irritant at high doses. Mild to moderate reversible skin irritation was observed in a dermal toxicity study XXXXXXXX. However, minimal irritation was observed in rabbits XXXXXXXX.
- In a repeat insult patch test in humans, XXXXXXXX produced neither skin irritation nor sensitisation. XXXXXXXX (90% SPS) was considered non-mutagenic in vitro.
- An eye irritation study in rabbits XXXXXXXX showed moderate redness and mild chemosis (swelling) of the conjunctiva within 1 hour of instillation. The iris and cornea were not affected. Irritation subsided within 24 hours.
- The MSDS for XXXXXXXX (90% SPS) indicated the possibility of irritation of the gastrointestinal tract from ingestion and mechanical irritation following eye exposure. Mild irritation may result from repeated or prolonged skin exposure.
- Submitted information noted the suitability for spray application with particle sizes greater than 50 µm. The information, however, also indicated that safety evaluations for spray applications with particle sizes less than 50 µm had not been conducted.
- A search of unpublished health and safety studies for SPS submitted to the US EPA (TSCATS database) records the submission of acute oral, dermal and inhalational toxicity, subchronic inhalation toxicity, skin and eye irritation studies (1985). These reports dated 1985 were included neither in the original submission nor in the additional information.
- SPS was not listed as a hazardous substance on the Australian Safety and Compensation Council List of Designated Hazardous Substances.

Based on the information above, the evaluation report made the following conclusion and recommendation:

- Overall, available information for SPS indicated a low toxicity profile. The high molecular weight of SPS would preclude significant dermal absorption.
- The chemical was anionic and, therefore, a potential skin and eye irritant. However, the chemical showed skin irritant effects in animals only at high concentrations. No skin irritation was observed during human patch testing. SPS (30%) induced reversible eye irritation in animals. The chemical was not mutagenic.
- Based on animal data, mild eye irritation may be possible from cosmetic products containing low concentrations of SPS. At concentrations currently used in cosmetic products (< 10%), available information indicates a likely low health risk from topical applications using pump sprays or gels. Pump sprays may represent a greater risk of eye contamination and irritation than gels. However, overall, the risk of eye irritation from normal use of products containing low concentrations of SPS, and the health risks in general, are low.

- The evaluation report therefore supported the revision of the scheduling for SPS to allow for cosmetic applications of SPS at low concentrations (eg. ≤ 10%).

The Committee noted a submission had been received from XXXXXXXX registering an interest in this issue.

The Committee agreed that the soluble form of SPS used for cosmetic applications did not warrant retention in Schedule 4. However, Members agreed that because of its anionic nature it was potentially a mild skin and eye irritant at high concentrations and should be in Schedule 5. The Committee also agreed that at low concentrations (≤ 10%) these risks were very low and did not warrant scheduling.

A Member noted that in the European Union there were warning statements to the effect of "do not spray near eyes". The Member questioned whether there was a need for any such warning statements for high concentrations of SPS i.e. those to be captured by the proposed Schedule 5 entry. The Committee generally agreed, however, that at most the risk was mild and that there was no need for specific safety directions or warning statements at this time.

The Committee also considered specifying the form of SPS to be covered by the Schedule 5 entry to the water-soluble non-cross linked form. However, Members noted that there did not appear to be any potential cosmetic use for the alternative cross-linked water-insoluble form that was used therapeutically and as such there was no need to specify the form in the Schedule 5 entry.

DECISION 2006/46 - 14

The Committee agreed, due to the potential for mild eye irritancy, to include sodium polystyrene sulphonate for cosmetic use in Schedule 5. The Committee further agreed to exempt low concentrations of sodium polystyrene sulphonate (≤ 10%) from the requirements of scheduling as these low concentrations posed very little risk.

Schedule 4 – Amendment

SODIUM POLYSTYRENE SULPHONATE – amend entry to read:

SODIUM POLYSTYRENE SULPHONATE for human therapeutic use.

Schedule 5 – New Entry

SODIUM POLYSTYRENE SULPHONATE in preparations for cosmetic use **except** in preparations containing 10 per cent or less of sodium polystyrene sulphonate.

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

6.1 PROHEXADIONE CALCIUM

PURPOSE

The Committees considered the scheduling of prohexadione-calcium.

BACKGROUND

The Committee noted that XXXXXXXX has applied for the approval of a new active constituent, prohexadione-calcium and registration of XXXXXXXX, a new water dispersible granular formulation (WG) for the suppression of shoot growth in apples. The product contains XXXXXXXX prohexadione-calcium, which inhibits certain stages of the biosynthesis of gibberellin. The resulting lower content of growth-active gibberellins leads to reduced longitudinal shoot growth. The product is formulated in XXXXXXXX.

Label restraints include warning against aerial application of the product, application of the product within 3 days of sprays containing calcium, ethylene or gibberellic acid, and application of the product more than 3 times per season.

DISCUSSION

The Committee considered an evaluation report from the Office of Chemical Safety which had assessed the data supplied in support of the approval of the active ingredient. In particular, the Committee noted that:

[Section deleted**]**

A member questioned whether prohexadione-calcium should be scheduled in a similar manner to its structural analogue trinexapac-ethyl (a Schedule 5 poison), noting that trinexapac-ethyl demonstrated evidence of squamous cell carcinoma of the non-glandular stomach in male rats and of skin in female rats. The member supported inclusion in Schedule 5.

Two members suggested that prohexadione-calcium could possibly be considered for exemption from scheduling on the basis of its low toxicity when judged against the Schedule 5 criteria. Although the substance was regarded as a slight to moderate eye irritant, it was argued that this aspect would be addressed by the product registration authorities through label warning statements.

The New Zealand member informed the Committee that New Zealand had considered prohexadione-calcium and had not regarded it as an eye irritant when judged against New Zealand criteria which were based on GHS.

DECISION 2006/46 - 15

The Committee agreed, having regard to the low acute toxicity and slight eye irritancy, that prohexadione-calcium be included in Schedule 5 of the SUSDP.

Schedule 5 - New entry

PROHEXADIONE CALCIUM.

6.2 FLORASULAM

PURPOSE

The Committee considered the scheduling of florasulam.

BACKGROUND

[Paragraphs deleted**]**

DISCUSSION

The Committee received from the Office of Chemical Safety an evaluation of the toxicological data submitted in support of the scheduling of florasulam and product registration. The Committee noted that:

[Section deleted**]**

Based on the low acute toxicity profile the OCS suggested that the NDPSC consider it appropriate to include florasulam in Schedule 5 (S5) of the SUSDP. There was no other significant toxicity associated with florasulam administration, it presented a low hazard from repeated use and was unlikely to produce irreversible toxicity. The main reason for not recommending its exclusion from scheduling was due to its slight skin and eye irritancy potential.

Extrapolation of data from similar SC product formulations containing either clopyralid or florasulam at the current product strength suggested that the acute toxicity of XXXXXXXX was not likely to be more than that described for florasulam technical. In addition, clopyralid is currently listed in S5 of the SUSDP. On this basis, an S5 classification is also appropriate for florasulam when present at XXXXXXXX with no cut-offs required.

The Committee agreed with the OCS assessment.

DECISION 2006/46 – 16

The Committee agreed, having regard to the slight skin and eye irritancy potential, that florasulam be included in Schedule 5 of the SUSDP.

Schedule 5 - New entry

FLORASULAM.

6.3 AMICARBAZONE

PURPOSE

The Committeee considered the scheduling of amicarbazone.

BACKGROUND

[Paragraphs deleted**]**

DISCUSSION

The Committee received the toxicological assessment which was undertaken by the Office of Chemical Safety (OCS). The OCS noted that studies submitted with the application formed a comprehensive toxicological database which is adequate to characterize the toxicological profile of amicarbazone. Most studies are recent, well-conducted and have been performed to contemporary toxicological standards. All data provided in these studies were relied on by the OCS in considering whether the approval of amicarbazone can be supported from a toxicological viewpoint.

The OCS toxicology assessment of amicarbazone noted the following:

[Section deleted**]**

Based on its toxicity profile, the approval by the APVMA of amicarbazone as a new active constituent was supported by the OCS.

Based on the acute oral LD_{50} of 1200 mg/kg bw in rats, the OCS has suggested that the NDPSC may consider it appropriate to include amicarbazone in Schedule 6 of the SUSDP.

DECISION 2006/46 - 17

The Committee agreed that based on the acute toxicity, amicarbazone be included in Schedule 6 of the SUSDP.

Schedule 6 - New entry

AMICARBAZONE.

7. MATTERS REFERRED BY OFFICE OF CHEMICAL SAFETY (OCS) BRANCH

7.1 INDUSTRIAL BIOCIDES

PURPOSE

The Committee considered:

(a) the current policy in relation to the scheduling of industrial biocides with a view to reconsidering the recent scheduling of N-tallow alkyl-1,3-propanediamine acetate & tallow alkylamine acetates into Schedule 6, and

(b) including industrial biocides in Appendix A to reflect the policy established by the Committee in August 1993 which excludes industrial biocides (except when available in the home) from scheduling.

BACKGROUND

In August 1993, the NDPSC considered a request from the then Chemical Safety Unit for advice as to whether industrial biocides would require poisons scheduling and, if so, what toxicological data would be required.

This request had arisen because, under the then newly established National Registration Scheme, the Chemicals Safety Unit would be responsible for the evaluation and approval of industrial biocides used in open and closed water cooling towers and processing plants, where the chemicals were being used as bactericides, algicides or slimicides.

The Committee considered that such industrial products did not require scheduling and should be assessed by the Chemicals Safety Unit/Worksafe as part of the registration process and be labelled in the context of their end use. However, where the product was to be available for use in the home, the Committee agreed that it would be referred to DPSSC for scheduling (and labelling) in the normal way. This policy remains current.

In June 2005, NDPSC (44) considered an assessment and referral from OCS for the scheduling of a new product XXXXXXXX which contained two new active constituents, N-tallow alkyl-1,3-propanediamine diacetate 325 g/L and tallow alkylamine acetate 26 g/L. The Committee was advised that the two active constituents required approval and poisons scheduling.

The two active ingredients are fatty nitrogen derived (FND) surfactants. Both are amine salts derived from tallow oil, and are mixtures of saturated hydrocarbons with varying

chain length (C11-C17). The mono-acetate was derived from a simple primary amine whereas the diacetate was a propylamine extended version of the mono-acetate. Both molecules are water soluble in their acetate salt form in contrast to their lack of solubility as free amines. They each exhibited surfactant-like properties because they possessed a positively charged polar 'head group' that bound to solid surfaces, leaving the long chain hydrophobic tail exposed.

The proposed use of C-Treat 6 in Australia involved treatment of land-based cooling systems utilising seawater for industry, hotels, and power station applications. The active constituents in the product function to control juvenile marine organisms (blue mussel, barnacle, chiton and fanworm) in seawater. The application stated that C-Treat 6 is not used as an antifouling paint and is not to be supplied to the public for use. Only trained personnel are permitted to use the chemical on customer sites.

The product was not intended for use on food crops or food-producing animals and no domestic use was suggested.

Following the recent publication of the outcome in relation to C-Treat 6, the APVMA raised the issue of apparent inconsistency between the recent decision in respect to the inclusion of N-tallow alkyl-1,3-propanediamine acetate and tallow alkylamine acetates in Schedule 6 and the decision taken in 2003 not to refer for scheduling, N-oleyl-1,3-diamineopropane and N-coco-1,3-diaminopropane which were similar products and proposed for similar use ie in the treatment of large industrial seawater cooling systems to control deposits, corrosion and marine growths. The decision not to refer N-oleyl-1,3-diamineopropane and N-coco-1,3-diaminopropane for consideration of scheduling was on the basis of the policy excluding industrial biocides from scheduling.

To establish certainty of decision, consistency in approach, and clarity for all stakeholders, the OCS has undertook to have:

- the NDPSC decision in regard to N-tallow alkyl-1,3-propanediamine acetate & tallow alkylamine acetates reconsidered in light of the use-pattern, toxicological profile and agreed industrial biocides policy, and
- the policy in relation to industrial biocides reflected in the SUSDP by proposing the inclusion of industrial biocides in Appendix A.

DISCUSSION

The Committee noted that, in regard to N-tallow alkyl-1,3-propanediamine acetate & tallow alkylamine acetates, the sponsor provided no toxicology data on either of the active constituents or the end-use product. According to the sponsor, the main active constituent N-tallow-1,3-propanediamine diacetate is formed "*in situ*" during manufacture, and no toxicological studies have been conducted on the chemical by the sponsor.

It was noted by the OCS that two chemically-related alkyl-ethoxylated propoxylated tallow amines, alkoxylated fatty alkylamine polymer (CAS No: 68213-26-3, trade names Armoblen 557 and Armoblen 600) with limited toxicology data, had previously been assessed by TGA. Its intended use was for thinning of stone fruit blossom and reducing the number of fruit set after flowering. Scheduling of this substance remains appropriate because it is used in agricultural production. Both substances were polymerisation products of tallow amine with ethylene and propylene oxide. The polymers had low oral toxicity and moderate inhalational toxicity in rats, and were slight irritant in rabbit eyes and skin. The polymers did not display genotoxic action in vitro. At the November 1998 meeting, alkoxylated fatty alkylamine polymer was included in Schedule 6 of the SUSDP, except in preparations containing 50% or less of it scheduled as S5, or in preparations containing 20% of less of it exempted from scheduling requirements.

Both N-tallow-1,3-propanediamine diacetate and tallow alkylamine acetates (fatty amine salts) belong to the fatty nitrogen-derived (FND) ether amines category of chemicals. These chemicals are comprised of hydrophobic and hydrophilic ends and act as surfactants by reducing surface tension and forming oil/water emulsions.

It was further noted that neither amines, tallow alkyl, acetates nor amines, N-tallow alkyltrimethylenedi-acetates were included in the SUSDP. The fatty nitrogen derived ether amines category of chemicals (fatty amines) was very similar in structure and function, with minimal differences among the alkyl substituents. The large database for the FND categories of chemicals suggested that the structural differences in these large alkyl chains did not appear to result in significant differences in toxicity or mutagenicity.

Based on the toxicological assessment described above, the OCS considered that the fatty nitrogen derived ether amines category of chemicals were of low oral toxicity, and were likely to have low to moderate acute dermal and inhalational toxicity. These chemicals were unlikely to be either mutagens or reproductive/developmental toxins. However, they were likely to be highly irritating and/or corrosive to the eyes, skin and mucosa.

The OCS therefore suggested that the NDPSC may consider it appropriate to include fatty nitrogen derived ether amines as a group (including amines, tallow alkyl, acetates and amines, N-tallow-alkyltrimethylenedi-, acetates) in Schedule 6 of the SUSDP. In making and agreeing to this proposal, the OCS and the NDPSC did not consider the agreed policy on industrial biocides which may have resulted in these substances being exempted from scheduling – if that policy was relevant to the substances under consideration.

The Committee considered that it appeared that in considering these matters, stakeholders were not generally aware of the policy in relation to industrial biocides. To avoid similar occurrences, the Committee agreed it would seem appropriate to reflect the policy in the SUSDP by including industrial biocides falling within the scope of the policy in Appendix A.

The Committee also noted that OCS suggestion that the NDPSC may also wish to consider whether these products (N-tallow alkyl-1,3-propanediamine acetate, tallow

alkylamine acetates, N-oleyl-1,3-diamineopropane and N-coco-1,3-diaminopropane) should be regarded as industrial biocides. On the basis that these products form a protective surface coating, the APVMA had noted that "these products are more like anti-fouling paints than they are like cooling tower treatments. They are mainly for biofouling prevention (including mussels, barnacles, chiton and fan worm) and not for Legionella". Label claims for these products include "for the treatment of freshwater cooling systems in hydroelectricity generating power stations to prevent corrosion, biofilm formation and attachment of freshwater organisms", "for the treatment of seawater cooling systems to prevent corrosion, biofilm formation and attachment of seawater organisms" and "for the control of blue mussel, barnacle, chiton and fanworm in seawater cooling systems".

The Committee noted public comment provided by XXXXXXXX who made the following observations.

- Industrial biocides currently fall within the definition of an agricultural chemical.
- Industrial biocides are supplied to and used in workplaces (rather than domestic settings).
- The Record of Reasons of Meeting 44 – June 2005 identified the Committees decision to include N-TALLOW ALKYL-1,3-PROPANEDIAMINE DIACETATE and TALLOW ALKYLAMINEACETATES in Schedule 6
- There are certain labelling considerations that may need to be taken into account for products that fall within the province of the Australian Pesticides and Veterinary Medicines Authority (APVMA). XXXXXXXX will be having further dialogue with the APVMA prior to the NDPSC meeting.

The XXXXXXXX representative stressed the need for consistency and that it was the view of the NDPSC that any substance considered by the APVMA should also be considered by the NDPSC.

The Committee agreed that the policy in regard to the consideration of biocides had worked well to date, particularly since biocides were a complex and diverse range of products. It was confirmed that the term biocides should be restricted to bacteriocides, algicides and slimicides though it was recognised that some sectors of industry saw 'biocides' as encompassing a much wider range of products. It was not the intention of the NDPSC (or the APVMA) to broaden the definition. The Committee further confirmed that biocides solely for industrial use did not need to come before the Committee although they would be assessed by the OCS.

The Committee agreed to maintain a watching brief in regard to substances for industrial biocide use and also on the appropriateness of the policy underpinning the approach towards the scheduling of industrial biocides.

DECISION 2006/46 - 18

It was further agreed to include bacteriocides, algicides and slimicides for industrial biocide use in Appendix A thereby clarifying the NDPSC's policy towards the exemption of these substances in this use situation.

The Committee also requested that N-oleyl-1,3-diamineopropane and N-coco-1,3-diaminopropane be considered for scheduling at the Committee's June 2006 meeting.

APPENDIX A – New Entry

ALGICIDES, BACTERIOCIDES OR SLIMICIDES for industrial use.

PHARMACEUTICALS

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

10.1 PHENYLEPHRINE

PURPOSE

The Committee considered post-meeting comment regarding the decision made at the October 2005 meeting to reschedule phenylephrine to harmonise with New Zealand.

BACKGROUND

Phenylephrine hydrochloride is a sympathomimetic with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without significant stimulating effects on the CNS at usual doses. Its pressor activity is weaker than that of noradrenaline but of longer duration. After injection it produces peripheral vasoconstriction and increased arterial pressure; it also causes reflex bradycardia. It reduces blood flow to the skin and to the kidneys. Phenylephrine and its salts are most commonly used, either topically or by mouth, for the symptomatic relief of nasal congestion. They are frequently included in preparations intended for the relief of cough and cold symptoms. For nasal congestion, a 0.25 to 1% solution may be instilled as nasal drops or a spray into each nostril every 4 hours as required, or phenylephrine hydrochloride may be given by mouth in doses up to 20 mg every four hours. In ophthalmology, phenylephrine hydrochloride is used as a mydriatic.

Phenylephrine was first considered by the Committee in August 1967. At that stage, all substances containing phenylephrine and its salts were put into Schedule 3. In January 1969, an exemption from scheduling was made to this entry for tablets or capsules containing 0.5% or less, for other preparations for internal use containing 0.1% or less and for substances, other than preparations for internal use, containing 0.5% or less. In May 1986, ophthalmic preparations containing 5% or more were made Schedule 4. In August 1991, parenteral forms of phenylephrine were added to the Schedule 4 entry. At the November 1999 Meeting, as a result of recommendations from the Trans-Tasman Harmonisation Working Party (TTHWP) which were considered at the February 1999 Meeting, the Committee amended the Schedule 2 entry for phenylephrine. It was noted at that meeting that the amendment only obtained partial harmonisation with New Zealand but the Committee decided that there should be no variation to the scheduling decision taken by the AHMAC Committee.

At the June 2004 Meeting, the Committee considered the TTHWP Decision 10/4 to remove phenylephrine from the 2-year list of unharmonised substances. At this meeting, the Committee noted that harmonisation efforts were focused on scheduling provisions and that differences in supply arrangements within both countries could lead to an

unharmonised approach in respect to supply. This is the case with phenylephrine because, despite consistency with scheduling provisions, nasal preparations containing phenylephrine will continue to be sold at airports in New Zealand. The Committee decided therefore to remove phenylephrine from the 2-year list.

DISCUSSION

Members recalled that at the October 2005 NDPSC Meeting, the Committee considered the scheduling of phenylephrine with a view to harmonising with New Zealand. The November 2004 Medicines Classification Committee (MCC) considered a submission from XXXXXXXX which proposed to amend the current scheduling of phenylephrine, expressed as a percentage to accommodate liquid dose forms, to allow a cut-off point of 10 milligrams or less per oral dose form for general sale and a pharmacy-only classification for solid dose forms containing more than 10 milligrams. The MCC recommended that phenylephrine for oral use should be a general sale medicine in products containing 50 milligrams or less per recommended daily dose and that this classification should be reviewed by a joint committee in two years. On the basis of the safety profile of oral phenylephrine (which is demonstrated in part by the lengthy market experience as a general sale item in the UK) and on the grounds of harmonisation with New Zealand, the October 2005 NDPSC Meeting agreed to amend the current Schedule 2 entry for phenylephrine to exempt oral preparations containing 50 mg or less per recommended daily dose (Decision 2005/45-14). The October 2005 NDPSC Meeting also agreed that the labelling issues raised by the MCC to reflect the limit on exempted use of phenylephrine for consumers under 65 years of age only should be referred to the Medicines Evaluation Committee (MEC) for consideration.

Members noted a correspondence from XXXXXXXX regarding the proposed label warning statement on the age restriction for exempt phenylephrine. Clarification was sought whether the restriction of the general sale phenylephrine to consumers under the age of 65 years was part of New Zealand's schedule entry.

Members were informed by the Secretariat that XXXXXXXX had accepted alternative advice on the MCC recommendation about the general sale classification of phenylephrine. Whilst Medsafe supported oral products containing no more than 50 mg phenylephrine per recommended daily dose being general sale medicine, it considered that a maximum pack size limit of 250 mg should apply. Medsafe also did not support restricting the general sale of phenylephrine to persons under the age of 65 years due to insufficient evidence. Members agreed that this updated information should be provided to the MEC for information and/or consideration.

DECISION 2006/46 - 18 (Confirmation of Decision 2005/45-14)

The Committee confirmed the scheduling amendment for phenylephrine (Decision 2005/45-14) which was to exempt oral preparations containing 50 mg or less per recommended daily dose with a maximum pack size of 250 mg of phenylephrine. The scheduling decision was made on the grounds of the safety of oral phenylephrine (which

was demonstrated in part by the lengthy market experience as a general sale item in the UK) as well as scheduling harmonisation with New Zealand.

Schedule 2 – Amendment

PHENYLEPHRINE – Amend entry to read

PHENYLEPHRINE **except:**

(a) when included in Schedule 4;

(b) in oral preparations containing 50 mg or less of phenylephrine per recommended daily dose in packs containing 250 mg or less of phenylephrine; or

(c) in topical eye or nasal preparations containing 1 per cent or less of phenylephrine.

10.2 PARACETAMOL

PURPOSE

The Committee considered an inadvertent omission from the paracetamol amendment in the October 2005 decision on RASML.

BACKGROUND

The warning statements and safety directions related to human medicines in the SUSDP Appendix F, Part 3 and "reverse schedule" entries (substances required to carry mandatory warning statements as a condition for exemption from scheduling) had been transferred, without alteration, to a new document, the *Required Advisory Statements for Medicine Labels* (RASML). The RASML was given legal effect in relation to medicines via the *Therapeutic Goods Order 69* (TGO 69 as amended by TGO 69A – effective 1 July 2004), which required medicines to include statements in accordance with the provisions of the RASML. A one-year transition period for existing products was provided and the RASML came into effect on 1 July 2005.

The February 2005 NDPSC Meeting considered a paper prepared by the Over the Counter (OTC) Medicines Section proposing consequential amendments to the SUSDP for consistency with the RASML. The Committee agreed that there was a need to retain the Appendix F, Part 3 entries for human therapeutic use until the Australia New Zealand Therapeutic Products Authority commences operation, including certain 'reverse scheduling' provisions specified in the Schedules for substances other than human therapeutic goods. The Committee also agreed to foreshadow the proposed amendments to the SUSDP for consideration at the June 2005 meeting.

The Committee did not proceed with the foreshadowed amendments to the SUSDP at the June 2005 Meeting due to concerns about a number of definitions. The October 2005 Meeting again considered the proposed amendments to the SUSDP and agreed to an out-of-session consideration to allow a detailed examination of the entries by the Drafting Advisory Panel. The Committee subsequentially agreed, out-of-session, to amendments to the SUSDP for consistency with the RASML. One of these amendments was to the Schedule 2 entry for paracetamol involving transfer of the warning statements to the RASML.

DISCUSSION

The Committee were advised that the Secretariat had discovered that part b) iii) and part c) iv) of the Schedule 2 entry for paracetamol had been omitted from the October 2005 RASML decision. Part b) iii) and part c) iv) required that products containing paracetamol could only be exempt from scheduling requirements if they were not labelled for the treatment of children aged 6 years or under.

The Members considered advice from the OTC Medicines Section that this omission occurred inadvertently in the RASML paper it presented to the February 2005 NDPSC Meeting and that there was at no time any proposal to remove these parts from the Schedule 2 entry for paracetamol.

DECISION 2006/46 - 19 (Variation to Decision 2005/45 – 15)

In accordance with sub-regulation 42ZCZ(3) of the *Therapeutic Goods Regulations 1990*, the Committee agreed to vary Decision 2005/45 – 15, part of which was an amendment to the Schedule 2 entry for paracetamol involving transfer of warning statements to the RASML, by amending the Schedule 2 entry for paracetamol through reintroduction of the clauses – part b) iii) and part c) iv) - that did not allow an exemption when labelled for the treatment of children 6 years or less which was inadvertently omitted from the October 2005 decision.

For implementation on 1 May 2006:

Schedule 2 – Amendment

PARACETAMOL for therapeutic use **except**:

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents when:

(i) enclosed in a primary pack that contains not more than 12 such powders or sachets of granules;

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

(iii) not labelled for the treatment of children 6 years of age or less; or

(c) in tablets or capsules each containing each containing 500 mg or less of paracetamol as the only therapeutically active constituent other than effervescent agents when:

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

(ii) in a primary pack of not more than 25 tablets or capsules;

(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 or less.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

11.1 PSEUDOEPHEDRINE

PURPOSE

The Committee reviewed the entry for pseudoephedrine in Appendix H of the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP).

BACKGROUND

The June 2002 NDPSC Meeting rescheduled all OTC single-active immediate release pseudoephedrine (PSE) preparations from Schedule 2 (S2) to Schedule 3 (S3) of the SUSDP to help reduce the problem of diversion to the illicit drug trade while maintaining access for legitimate users. The October 2004 NDPSC Meeting considered rescheduling the remaining S2 PSE preparations to S3. The October 2004 NDPSC Meeting agreed to take no scheduling action at that time, in order to allow time for initiatives implemented by government, industry and pharmacy organisations to take full effect. The February 2005 NDPSC Meeting continued its consideration of illicit diversion of PSE and again noted the various initiatives in place through the NSW Poisons Advisory Committee, the

Pharmacy Guild of Australia and the Australian Self-Medication Industry. Again, the Committee agreed to allow more time to determine the effectiveness of these initiatives and so expressed its intent to reconsider the scheduling of PSE at the June 2005 Meeting.

At the June 2005 Meeting, on the basis of the available information and in the interest of public health and safety, the Committee agreed to reschedule the majority of pseudoephedrine products to S3, with liquid preparations containing more than 800 mg pseudoephedrine hydrochloride (or its equivalent) per pack or other preparations containing more than 720 mg pseudoephedrine hydrochloride (or its equivalent) per pack becoming S4 medicines. This initial decision was based on the fact that PSE is the essential precursor for methamphetamine production, that the harm associated with methamphetamine is considerable and that rescheduling should reduce the illicit diversion while retaining accessibility to legitimate consumers. The Committee also agreed to remove pseudoephedrine from Appendix H of the SUSDP, considering that such action was in line with the re-scheduling of pseudoephedrine because of public health concerns with diversion.

At the October 2005 Meeting, the Committee agreed to vary the initial decision from the June 2005 Meeting by implementing it in two stages: the first stage being the removal of all remaining S2 products (slow-release, combination and undivided preparations) to S3 (implementation date 1 January 2006) and the second stage being to reschedule all liquid preparations containing more than 800 mg of pseudoephedrine hydrochloride (or its equivalent) and all other preparations containing more than 720 mg of pseudoephedrine hydrochloride (or its equivalent) to S4 (implementation date 1 April 2006). The Committee also agreed not to remove pseudoephedrine from Appendix H of the SUSDP. The Committee felt that it was reasonable for the advertising status quo to remain, at least initially, to allow consumers to be informed of the impact of the scheduling changes. Advice on advertising was sought from XXXXXXXX.

DISCUSSION

Members noted advice from XXXXXXXX which was received just before the meeting. It was the view of XXXXXXXX that retaining the current entry for pseudoephedrine in Appendix H of the SUSDP was in the public interest. A number of reasons were provided by XXXXXXXX to support its view. These reasons included:

- there is no evidence to suggest that the advertising of S3 products containing pseudoephedrine stimulates diversion for illicit use, since all of these products are within pharmacies, must be physically out of reach of consumers, and access is provided only under supervision and advice of a pharmacist or doctor.

- other proactive measures are being undertaken by pharmacy to address the diversion problem, such as “Project Stop”.

Members agreed that retaining direct-to-consumer advertising of pseudoephedrine products should ensure consumers’ awareness of the scheduling changes and the need for

the pharmacist to be involved in their sale. In addition, it was noted that by retaining pseudoephedrine in Appendix H, newer alternative Schedule 2 products that are based on phenylephrine will be able to advertised as "pseudoephedrine free". The Committee reconfirmed its view that the pseudoephedrine scheduling measures would effectively reduce the amount of pseudoephedrine diverted from pharmacies into illicit methamphetamine manufacture, and agreed that advertising itself should not stimulate diversion for illicit use. Hence, it was reasonable for the direct-to-consumer advertising status for pseudoephedrine to remain at this stage.

OUTCOME

The Committee agreed to retain pseudoephedrine in Appendix H of the SUSDP at this stage, to allow consumers to be informed through advertising of the impact of the scheduling changes and available S3 pseudoephedrine products.

11.2 SEDATING ANTIHISTAMINES (BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DIPHENYLPYRALINE, DOXYLAMINE, PHENIRAMINE, THENYLDIAMINE, TRIMEPRAZINE, TRIPROLIDINE)

PURPOSE

The Committee considered the foreshadowed decision from the October 2005 meeting relating to sedating antihistamines.

BACKGROUND

The October 2002 meeting of the Trans-Tasman Harmonisation Working Party (TTHWP) recommended that New Zealand harmonise with Australia on the scheduling of antihistamine preparations combined with other active ingredients including codeine, paracetamol and pseudoephedrine using the following broad principles (TTHWP Decision 8/8):

(i) antihistamines and preparations with a significant potential for abuse be included in S4/Part 1;

(ii) single-active preparations of sedating antihistamines be included in S3/Part II; and

(iii) single-active preparations of non/low-sedating antihistamines and specified combination preparations of antihistamines be included in S2/Part III.

The October 2003 NDPSC Meeting agreed to foreshadow consequential amendments to the SUSDP to align scheduling with the registration status of existing products while maintaining consistency with the recommendations of TTHWP Decision 8/8.

The February 2004 NDPSC Meeting accordingly amended the SUSDP S2 entries as foreshadowed for sedating antihistamines such that the S2 entry for diphenhydramine and other oral sedating antihistamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenylpyraline, doxylamine, pheniramine, promethazine, thenyldiamine, trimeprazine and triprolidine) were amended to address the concerns about the sedating effects of the antihistamines. Consequently, preparations for the treatment of symptoms of coughs, colds or influenza when combined with a sedating antihistamine were classified as S2 with at least one of the other therapeutically active substances was a sympathomimetic decongestant or when in a day-night pack with the dose containing the sedating antihistamine was labelled for bed-time dose. This amendment was given effect from 1 September 2004.

The February 2005 NDPSC Meeting considered XXXXXXXX proposal to amend the scheduling of diphenhydramine and re-instate in S2 two of its affected products containing diphenhydramine which were rescheduled to S3 because they did not contain a sympathomimetic. One was a single-active product containing diphenhydramine as cough suppressant and the other was a cough and cold preparation combined with dextromethorphan. XXXXXXXX proposed that products for the treatment of the symptoms of coughs, colds or influenza containing diphenhydramine that did not contain a sympathomimetic decongestant as one of the therapeutically active substances but combined with other active ingredients such as an antitussive or expectorant should remain in S2 while retaining hypnotic preparations in S3. The Committee also noted that the November 2004 MCC meeting had agreed to accept the broad principles of the NDPSC with regard to the classification of sedating antihistamines but raised a few issues which MCC thought were not considered by the NDPSC. The MCC advised that it had decided to delay the implementation of the scheduling amendments relating to antihistamines to allow a further round of public consultation on the proposed schedule wording for each individual antihistamine. In light of the submissions received and in anticipation of the outcomes of the May 2005 MCC meeting, the Committee agreed to review the scheduling of antihistamines at the June 2005 meeting.

The June 2005 NDPSC Meeting noted that the June 2005 MCC Meeting agreed to harmonise with Australia on the scheduling of sedating antihistamines except for mepyramine, for which a separate recommendation had been proposed for consideration of the NDPSC (see item 16.1.2). On the grounds of harmonisation and taking into account the public health concerns regarding the potential risks associated with the sedative effects of the antihistamines, the Committee confirmed that the scheduling of sedating antihistamines amended at the February 2004 meeting remained appropriate.

The October 2005 NDPSC Meeting considered a submission from XXXXXXXX which highlighted the issue that night-time doses of medicines containing sedating antihistamines that were not combined with a sympathomimetic decongestant were included in S3. Furthermore, XXXXXXXX advised that there were a number of combination sedating antihistamine products on the ARTG which contained a sympathomimetic decongestant or phenylephrine with or without paracetamol. Given

that such products were indicated for the symptomatic treatment of conditions **other than** coughs, colds or flu, they remained within S3 even if such products had addressed the Committee's concerns regarding the sedation risks of formulations containing sedating antihistamines. The Committee concurred with the points raised in XXXXXXXX submission and agreed to foreshadow an amendment to the sedating antihistamine S2 entries to remove references to indications. This foreshadowed decision would then allow all combination preparations containing a sympathomimetic decongestant (i.e. phenylephrine) to be considered S2 substances, irrespective of indications. In addition, the NDPSC referred cyclizine for the prevention of travel sickness to the TTHWP for initial consideration in light of MCC's advice that cyclizine had been reclassified to Restricted Medicine in New Zealand (i.e. S3) because of sedation potential (cyclizine was S4 in Australia). The TTHWP recommendation regarding cyclizine under item 1.8.2.1 of the agenda was considered under item 11.2.1 as part of sedating antihistamines in travel sickness products.

Furthermore, the October 2005 NDPSC Meeting also agreed to amend the wording of the entries for sedating antihistamines to clarify the Committee's intent in regards to the statement "2 years of age or less" which meant 2 years from the day of birth. This statement would be replaced with "under two years of age" to clarify the entry.

DISCUSSION

The Committee noted the pre-meeting submissions received from XXXXXXXX supporting the removal of references to indications in the S2 entries of the sedating antihistamines. XXXXXXXX also highlighted the issue that the statement "**except** in preparations for the treatment of children two years of age or less" in the foreshadowed decision, if read in isolation, could suggest that products labelled for use in children 2 years of age and under were unscheduled medicines.

It was noted that promethazine and diphenhydramine's S2 entries included travel sickness products and were also discussed under item 11.2.1 (sedating antihistamines in travel sickness products). However, given that the resulting amendments for these two substances related only to the removal of the indications and re-wording of the age restriction, the amended entries for promethazine and diphenhydramine were included under this item for clarity.

DECISION 2006/46 - 20

The Committee agreed to amend the entries for the sedating antihistamines listed below to remove from the S2 entries references to indications and clarify the wording in relation to the age restriction. Furthermore, the Committee agreed to recommend that MCC consider adopting the sedating antihistamine entries on the grounds of harmonisation.

Schedule 2 - Amendments

BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DIPHENYLPYRALINE, 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; and

(c) not labelled for the treatment of children under 2 years of age.

DIPHENHYDRAMINE, PROMETHAZINE - Amend entries to read:

[SUBSTANCE] in oral preparations:

(a) in primary packs of 10 doses 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; and

(iii) not labelled for the treatment of children under 2 years of age.

PHENIRAMINE – amend entry to read:

PHENIRAMINE:

(a) in eye drops;

(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; and

(iii) not labelled for the treatment of children under 2 years of age.

THENYLDIAMINE – amend entry to read:

THENYLDIAMINE:

(a) in nasal preparations for topical use; 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 thenyldiamine in the bed-time dose; and

(iii) not labelled 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; and

(c) not labelled for the treatment of children under two years of age.

Schedule 3 – Amendment

TRIMEPRAZINE – Amend entry to read:

TRIMEPRAZINE:

(a) in solid oral preparations **except** when included in Schedule 2; or

(b) in liquid oral preparations containing 10 mg or less of trimeprazine per 5 mL.

11.2.1 SEDATING ANTIHISTAMINES IN TRAVEL SICKNESS PRODUCTS (CYCLIZINE, DIMENHYDRINATE, DIPHENHYDRAMINE, MECLOZINE AND PROMETHAZINE)

PURPOSE

The Committee considered harmonisation of the scheduling of sedating antihistamines in travel sickness products, i.e. cyclizine, dimenhydrinate, diphenhydramine, meclozine and promethazine.

BACKGROUND

At the February 2004 NDPSC meeting consideration of sedating antihistamines, members also noted that sedating antihistamines in travel sickness products in S2 were already harmonised with New Zealand except meclozine. For completeness, the February 2004 NDPSC meeting accordingly agreed to foreshadow the inclusion of a new entry in S2 for small packs of meclozine travel sickness products to harmonise with New Zealand and for consistency with the scheduling of other travel sickness products in the SUSDP. There were no meclozine travel sickness products registered for supply in Australia at the time but there was one travel sickness product registered in New Zealand.

The October 2005 NDPSC meeting also considered separately the scheduling of dimenhydrinate which was identified in the OZNZ Scheduling database as unharmonised with New Zealand because of the age restriction specified in the S2 entry. This meant that preparations for the prevention or treatment of motion sickness when in packs each containing 10 doses or less for use by children under 2 years of age were S3 in Australia (except trimeprazine) while remaining Pharmacy Only medicines in New Zealand. To address this harmonisation issue, the October 2005 NDPSC meeting asked the Secretariat to investigate if the *Required Advisory Statement for Medicines Label* (RASML) required a warning statement restricting the use of sedating antihistamines in S2 to children aged 2 years and over. If the RASML already provided this warning, the Committee felt inclined to consider the option of removing the age restriction in the entry for dimenhydrinate as well as from other sedating antihistamines in S2 at the February 2006 meeting.

The October 2005 NDPSC meeting considered comment from the June 2005 MCC Meeting (in italics below) in relation to the NDPSC's recommendations to harmonise the scheduling of oral sedating antihistamines which were amended in February 2004.

A. *That the NDPSC should be asked for clarification of why sedating antihistamines for travel sickness have remained classified as S2 medicines when they contain only a sedating antihistamine.*

At the October 2005 NDPSC meeting, members recalled that the NDPSC retained in S2 diphenhydramine, dimenhydrinate and promethazine for the prevention or treatment of motion sickness in adults and children aged 2 years and above, when in primary packs containing 10 tablets or less, on the grounds that the scheduling of these entries were harmonised with New Zealand.

B. *That the exemption for the sale of meclozine for travel sickness at travel terminals or aboard ships or planes should retain the pack size of 12 tablets and that the NDPSC should be asked to harmonise on this pack size for OTC sales.*

The Committee agreed to foreshadow at the February 2004 NDPSC Meeting the adoption of the New Zealand OTC entry in Schedule 2 for meclozine for the prevention or treatment of motion sickness in a pack containing 12 or less tablets or capsules. In addition, the age restriction not to use the medicine on children under 2 years of age was included in the foreshadowed S2 entry for meclozine for consistency with other sedating antihistamines in the SUSDP. The foreshadowed decision was confirmed at the June 2004 NDPSC meeting to harmonise with New Zealand and prior to this, meclozine was a Prescription Only medicine in Australia. The current scheduling for meclozine was harmonised with New Zealand in terms of pack size and differed only in the age restriction specified in all S2 sedating antihistamine entries.

The June 2005 MCC minutes indicated that it would be considering the classification of sedating antihistamines for use in children under the age of two years at its next meeting with a view to possible reclassification to prescription medicine.

Secretariat's note: Sedating antihistamines for use in children under the age of two years are S3 medicines in Australia.

C. *That cyclizine for the prevention of travel sickness should be reclassified as a restricted medicine in New Zealand (i.e. S3) and that the NDPSC be notified of this recommendation.*

See agenda item 1.8.2.1 for the discussion and decision on cyclizine.

D. *That mepyramine should be classified as a prescription medicine except for dermal use and a pharmacy-only medicine for dermal use and that the NDPSC should be asked to harmonise with the New Zealand classification.*

Mepyramine would be dealt with as a separate item under 16.1.2.

DISCUSSION

The Committee noted that XXXXXXXX in its pre-meeting comment stated that the requirement for specific warning statements for dimenhydrinate should be considered as part of the registration process. XXXXXXXX had also asked to be kept informed of any outcomes and for the opportunity to provide comment during the post-meeting period should specific issues arise in relation to meclozine.

The Committee was advised that the RASML (June 2005 version) did not include label statements relating to age restrictions for S2 sedating antihistamines and it was proposed that the Committee recommend that New Zealand adopt the age restriction specified in all sedating antihistamine entries in S2 to fully harmonise the entries.

The Committee recalled that the February 2004 NDPSC meeting decision to retain the scheduling of travel sickness products was based primarily on the jurisdictions' strong support for the continued availability of travel sickness products in bus stops, ferry terminals, airports, etc. and on the basis that there was no mechanism under State/Territory legislation to allow such supply to occur within the S3 environment. In supporting this approach, the Committee assumed that New Zealand would similarly retain travel sickness products in S2, given their harmonisation status, and thus exempting them from TTHWP Decision 8/8 which recommended that single-active preparations of sedating antihistamines be included in S3/Part II. Jurisdictional members indicated that given the lack of evidence to indicate that small packs of travel sickness products were the subject of abuse, members' support for travel sickness products in small packs to remain available as S2 medicines remained unchanged, except cyclizine.

The Committee was advised that MCC had foreshadowed the inclusion of oral sedating antihistamines for use in children under 2 years of age in S4. Members were of the view that it may be appropriate for the NDPSC to recommend that New Zealand consider including sedating antihistamines for use in children under two years of age in S3, unless there was evidence of harm associated with this level of availability, to harmonise with Australia.

OUTCOME

The Committee agreed that sedating antihistamines in small packs for use in the treatment or prevention of travel sickness remain in S2 except for cyclizine in oral preparations which the Committee had agreed to include in S3 (see agenda item 1.8.2.1) to harmonise with New Zealand.

11.3 AMISULPRIDE

PURPOSE

The Committee considered the foreshadowed decision to include amisulpride in Appendix K of the SUSDP.

BACKGROUND

Amisulpride is an atypical antipsychotic of the benzamide class. It is indicated for the treatment of acute and chronic schizophrenic disorders in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as

blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

Amisulpride was included in Schedule 4 at the November 2000 NDPSC Meeting on the grounds of harmonisation with New Zealand and that it was a new substance and the condition being treated required medical management.

The June 2005 NDPSC Meeting considered the foreshadowed decision to include amisulpride in Appendix K of the SUSDP. A pre-meeting submission from XXXXXXXX opposed its inclusion in Appendix K, with the following points highlighted:

- 50 – 400 mg amisulpride did not impair performance in controlled, double-blind, randomised study settings.
- The sedation incidence of amisulpride would expected to be low due to its strong affinity for D2 and D3 receptors.
- An article by Prof Nicholas Keks (2004). This article reproduced a table which appears in Therapeutic Guidelines: Psychotropic. This tabulation indicates that sedation is infrequently reported for amisulpride.

At the time, the Committee found it difficult to evaluate the sedation potential of amisulpride. A concern was expressed that inclusion of a substance in Appendix K that may not cause drowsiness would dilute the importance of the sedation warning label. Due to the conflicting information from the available data, PI and CMI documents for amisulpride relating to its sedating potential, the Committee agreed to defer consideration of this matter and seek expert advice from XXXXXXXX.

DISCUSSION

The Committee noted that this matter had been gazetted and that no public submissions had been received. Members understood that XXXXXXXX wrote in response to the October 2005 NDPSC meeting gazette notice advising that they wish to comment when the XXXXXXXX review is completed and reported to NDPSC.

Members noted that the October 2005 XXXXXXXX Meeting considered the enquiry regarding inclusion of amisulpride in Appendix K of the SUSDP. XXXXXXXX supported the inclusion of amisulpride in Appendix K based on the following evidence derived from the PI, CMI, APF, Clinical Evaluation Report and the sponsor's submission:

- It may affect reaction time in driving/operating machinery, and may cause drowsiness in some people. (PI & CMI)
- It may enhance the effects of CNS depressants. (PI)
- Amisulpride has similar rates of somnolence as haloperidol, flupenthixol and risperidone (e.g. 3% for amisulpride *vs* 4% for haloperidol). (CER & PI)
- Although 50 – 400 mg of amisulpride did not impair performance in controlled, double-blind, randomised study settings, dosage of 400mg/ day impaired

psychomotor and cognitive tasks. However, the usual daily dose for amisulpride is 400 – 1000mg for positive symptoms.

- There are no pharmacokinetic or pharmacodynamic interactions between amisulpride (single dose of 50 mg and 200 mg) and alcohol. (CER)
- The incidence of sedation would expected to be low due to its strong affinity for D2 and D3 receptors and low affinity for H receptor subtypes. XXXXXXXX noted that such a deduction was only based on theory from *in vitro* studies and is no substitute for clinical data.
- Keks (2004) paper shows that the sedation frequency for amisupride is between 2% and 10%. XXXXXXXX noted this figure does not reflect the intensity of the effect. It is same as fluphenazine salts or esters, haloperidol bases or esters, trifluoperazine and flupenthixol decanoate.

Members noted XXXXXXXX view that there are no established criteria for a drug to be included in Appendix K of the SUSDP and thus, in the absence of such criteria, the recommendation is made based on precedence. XXXXXXXX concluded that if haloperidol, fluphenazine, trifluoperazine and flupenthixol are included in Appendix K, amisulpride should be included as well, given that it induces sedation at about the same frequency as the aforementioned drugs. The Committee noted that haloperidol, fluphenazine and trifluoperazine are currently listed in Appendix K. Hence, the Committee decided to include amisulpride in the Appendix K of the SUSDP at this stage for a consistent point of view and based on comparison of similar sedative effects between these medicines.

DECISION 2006/46 - 21

The Committee agreed to include amisulpride in Appendix K of the SUSDP based on the inclusion in Appendix K of haloperidol, fluphenazine and trifluoperazine which have a similar sedative effect.

Appendix K – New entry

Amisulpride.

11.4 BLOOD PRODUCTS – APPENDIX A

PURPOSE

The Committee considered the foreshadowed decision to exempt fractionated plasma products and recombinant blood products from scheduling requirements through inclusion in Appendix A of the SUSDP.

BACKGROUND

Historically, the Committee had a standing policy of not scheduling blood products, given that scheduling may place unwarranted restrictions on the supply of products which

already have adequate Commonwealth and State/ Territory controls. At the February 2005 Meeting, the Committee looked at the recommendations arising from the Review of the Australian Blood Banking and Plasma Product Sector. This Review was considered in the context of considering a general exemption (Appendix A) for blood products for therapeutic use. The Committee was satisfied at this meeting that appropriate regulatory mechanisms were in place to warrant the exemption of blood products from scheduling requirements and agreed to foreshadow the inclusion of blood products in Appendix A of the SUSDP.

Comment that XXXXXXXX provided in May 2005 stated that it would seem illogical to exempt products derived from blood and not equivalent recombinant products, especially considering some are only available as recombinant products (eg Factor VIIa). XXXXXXXX stated that previously, XXXXXXXX manufactured most plasma derived product and this was distributed by the Australian Red Cross Blood Service (ARCBS). More recently, foreign manufactured products became commercially available directly from sponsors and this situation could only increase. XXXXXXXX also noted that plasma-derived products were intended for the treatment of serious disease and as such require medical supervision and so should not be exempt from scheduling. XXXXXXXX also provided comment to the June 2005 NDPSC meeting.

At the June 2005 Meeting the Committee concluded that hospitals and health services have policies and guidelines in place to ensure best practise in the supply and use of blood and blood products and these controls obviate the need for scheduling controls. Furthermore, the Committee felt it inappropriate and impractical for a pharmacist to dispense such product, particularly in an emergency setting. However, the Committee was conscious of the shift in supply arrangements of plasma derived products, including foreign-manufactured and recombinant blood products. Thus the Committee agreed to include an entry in Appendix A of the SUSDP for whole blood and blood components (effective 1 January 2006) but to foreshadow the consideration of the scheduling of fractionated plasma and recombinant blood products at the October 2005 Meeting. The Appendix A entry for whole blood and blood components came into effect on 1 January 2006.

At the October 2005 Meeting the Committee agreed not to include fractionated plasma products and recombinant blood products in Appendix A but to instead seek input from XXXXXXXX on the possible ramifications of scheduling such products and to consider this input, along with other public submissions, at the February 2006 Meeting.

DISCUSSION

The Committee noted that a number of public submissions had been received in relation to this matter following gazettal. They included a submission from the XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX and the XXXXXXXX.

Members noted the submission from the XXXXXXXX which made the following points in favour of an exemption for fractionated blood products:

- Currently, fractionated blood products are handled by staff within a hospital or blood bank that hold the required skills to manage such product and not by pharmacy staff.
- Access to such products is required 24 hours a day, 7 days a week. There is concern that access via pharmacy may therefore compromise patient care.
- As rapid access to such product is essential, broader distribution through pharmacies may result in more stock expiring. Given that such product is sourced from plasma of blood donors, replacement of such product is difficult.
- XXXXXXXX staff provide a gate-keeper role for product that is in short supply and requests for such products are reviewed by a medical officer. Such a safety net would not exist if these products were supplied via pharmacies.
- Blood component products and plasma-derived products are usually supplied simultaneously and this is both simple and cost effective. Scheduling plasma-derived products would require development of new ordering systems.
- Scheduling plasma-derived products would not add value to the health system and may indeed lead to deterioration in optimal patient care.

The Committee noted the pre-meeting submissions from the XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, and XXXXXXXX raised similar points mainly relating to the potential impact should fractionated plasma products and recombinant blood products were included in Schedule 4. The points raised were summarised as follows:

- Scheduling these products would be unnecessary given the mechanisms already in place for the oversight and management of the national blood supply, including the supply of blood products and recombinant blood products by XXXXXXXX and XXXXXXXX.
- Products for treatment of specific conditions like haemophilia which are managed by specialist doctors and nurses in hospital settings or through haemophilia treatment centres (HTC) are associated with low risks. Scheduling these products could adversely impact on patients who are being treated through home therapy programs managed by the HTC. No cases of inappropriate distribution to the public have been reported to XXXXXXXX.
- Hospital blood banks have extensive expertise with inventory of blood products including traceability and appropriate use. Any change to the current system (ie a scheduling change) resulting in delays or restrictions on the availability of products to patients could adversely impact on patient care and potentially lead to increased morbidity and mortality. Furthermore, broadening distribution networks via pharmacies may result in increased costs.
- The gate-keeper role managed by the ARCBS ensures that use of short-supply products is closely scrutinised and they often order both blood components and

plasma-derived product for the same delivery. This system ensures simplicity in the context of ordering and efficiency in the context of logistics.

- There should be a consistent approach to scheduling/exemption of fractionated plasma products and recombinant blood products. It was highlighted that "IMMUNOGLOBULINS for human parenteral use **except** where separately specified in these Schedules." is currently listed in Schedule 4 of the SUSDP. While in contrast to the immunoglobulin products, haemostasis plasma products (eg Factors XVIII, IX etc) or albumin are not listed in Schedule 4.
- Given the move to the Australia New Zealand Therapeutic Products Agency, there may be value in exploring the New Zealand arrangements for the scheduling and distribution of these products, noting that the scheduling of some of these products in New Zealand is supported by a broader licensing program that allows products to be distributed in a manner comparable to that currently in place in Australia.
- Other than consultation with XXXXXXXX and the XXXXXXXX, concern was expressed in that consultation with the wider Australian Blood Sector has been inadequate. Stakeholders consider that there has been no opportunity to examine the potential impact of scheduling changes or to identify other means of improving governance arrangements.

XXXXXXXX recommended to the Committee that a period of consultation of 12 months be agreed by NDPSC to allow input by key stakeholders to be taken into account. XXXXXXXX indicated that it would be willing to work with the NDPSC to facilitate such consultation, where possible, if the NDPSC were to do the consultation in conjunction with a XXXXXXXX Working Party. The following points were further noted in the XXXXXXXX submission:

- Jurisdiction A considered thirty-one (31) products to be 'fractionated blood products' or 'recombinant blood products' under the national blood arrangements. It was highlighted that some blood products were already classified as Schedule 4 medicines i.e. all the hyperimmune Igs XXXXXXXX, IVIG XXXXXXXX and XXXXXXXX. The products that were unscheduled included XXXXXXXX, and other plasma volume expanders XXXXXXXX. In addition, the XXXXXXXX submission indicated that XXXXXXXX was of the view that "…..the pathology sector is already 'dispensing' S4 drugs, so any further inclusion of products under S4 could see a proposal for no change to current arrangements".
- XXXXXXXX questioned the validity of the arguments made by XXXXXXXX. XXXXXXXX did not consider the supply of recombinant clotting factors to be tightly regulated as they are routinely delivered directly to the patient and review by a doctor is not a requirement of ongoing supply. Additionally, XXXXXXXX had concerns with the gate keeping role play by the XXXXXXXX in relation to fractionated plasma products, principally IVIg.

The submission received from XXXXXXXX raised the following points:

- The TGA regulates the quality, safety and efficacy of blood products and recombinant blood products by a combination of pre-market and post-market controls. The TGA also regulates the quality and safety of fresh blood and blood components principally through compliance with product standards and manufacturing controls. Fresh blood and blood components, unlike blood products are not included in the Australian Register of Therapeutic Goods (ARTG) prior to supply.
- There is a need to clarify the terminology used for blood components and blood products as the terms are sometimes used interchangeably. A flow chart showing the relationship between whole blood, fresh blood components and blood products (manufactured from fresh blood components including plasma products) was provided.
- There needs to be an understanding of the various supply channels and whether there are variations between jurisdictions. The current system of distribution and supply has developed over the years and has met the needs of clinicians and patients but is not underpinned with any formal mechanism. With the increase in the number of overseas manufactured blood products and comparable recombinant products and the entry of additional suppliers there is a potential for inappropriate distribution and use to occur outside the current suppliers and distribution arrangements. On this basis, it would be important to regularise and formalise current arrangements nationally and this may be achieved through formal recognition of a system for assessment and authorisation for treatment and monitoring of therapy by medical practitioners of blood products and recombinant blood products through a network of approved clinics or distribution agencies. For example, supply through the ARCBC to be overseen by the NBA and the JBC. If this occurs, the intent of scheduling could be met.

The Committee was informed that the Secretariat had subsequently written to XXXXXXXX seeking the product (including the active ingredient) list of fractionated / recombinant blood products distributed under XXXXXXXX. Members noted that a detailed inventory of both products and presentation sizes currently active in the National Blood Supply Chain was provided for the Committee's consideration by XXXXXXXX. The Committee noted that the list showed a mixture of both prescription and unscheduled products and there appeared to be no common criteria in the way products were included or excluded from the SUSDP.

The Committee discussed the following issues:

- Fractionated plasma and recombinant blood products should be reviewed to determine how these products are being supplied and identify those which may require to be regulated through scheduling based on known risks and pattern of use. Members were mindful that scheduling fractionated plasma and recombinant blood products used solely within the hospital setting was not the intent of the Committee and that the Committee would be focusing on specific products appropriate for making available only through prescription by a medical practitioner including those which have potential for abuse.

- Members noted that there was a need for a policy or guidelines to be established to assist the Committee in determining what type of fractionated plasma and recombinant blood products should be considered for scheduling vs. those which should remain exempt from scheduling on the basis that their supply is adequately controlled through other mechanisms. Members noted that under current arrangements, there were no clear criteria for the inclusion or exclusion of substances from the SUSDP and the information in the XXXXXXXX minutes did not include advice on the likely distribution and supply of blood products considered for registration. In addition, members agreed that blood products already listed in S4 such as heparins, lepirudin, monoclonal antibodies and immunoglobulins should be reviewed to determine the need for their continued inclusion in S4 as well as rationalise the rest of the products in the XXXXXXXX summary to determine whether a formal exemption via Appendix A was appropriate for products considered to not require scheduling.
- Members agreed with XXXXXXXX in that there was a need to understand the current distribution and supply arrangements for fractionated plasma and recombinant blood products and implement a cohesive regulatory system and uniform national approach for managing the distribution and supply of such products and reduce the potential for inappropriate access.

OUTCOME

To assist the Committee in developing a strategy for dealing with fractionated plasma and recombinant blood products from a scheduling point of view and understand how scheduling would fit into current control frameworks, members agreed to seek further advice from XXXXXXXX. The Committee agreed that as a starting point, it would take the same approach taken for medical devices whereby the list of products provided by XXXXXXXX would be referred to XXXXXXXX for advice on their pattern of use and regulatory arrangement for their distribution and supply. Those products assessed on a case-by-case basis as requiring inclusion in the SUSDP would be considered for retention in the SUSDP (or added to), while those not requiring scheduling would be considered for exemption from the requirements of scheduling via Appendix A.

11.4.1 OCTOCOG ALFA

At its 237th meeting in December 2004, the ADEC considered a submission from XXXXXXXX to register XXXXXXXX, containing the new chemical entity octocog alfa (rch) XXXXXXXX. The proposed indication was “for use in haemophilia A for prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with Advate as peri operative management. Advate is not indicated in von Willebrand’s disease”. Octocog alfa (rch) was designated as an Orphan Drug for the proposed indication.

[Paragraphs deleted**]**

OUTCOME

The Committee deferred consideration of this item to the June 2006 meeting when the development of a policy position on the scheduling of fractionated plasma and recombinant blood products would be further considered by the Committee.

11.4.2 HUMAN PLASMA-DERIVED PROTEIN C

The June 2004 ADEC Meeting recommended the approval of the application submitted by XXXXXXXX to register XXXXXXXX, containing plasma-derived human protein C XXXXXXXX, indicated for the treatment of purpura fulminans and coumarin-induced skin necrosis in patients with severe congenital protein C deficiency.

Protein C is an endogenous inhibitor of blood coagulation. A preparation of protein C purified from human plasma is used in the management of thromboembolic disorders in patients with congenital deficiency of protein C.

OUTCOME

The Committee deferred consideration of this item to the June 2006 meeting when the development of a policy position on the scheduling of fractionated plasma and recombinant blood products would be further considered by the Committee.

11.5 DEFINITION OF COMPOUNDED

PURPOSE

The Committee reviewed the SUSDP entries which used the definition “compounded”.

BACKGROUND

The February 1991 NDPSC Meeting, XXXXXXXX, foreshadowed a definition of compounded “*combined with one or more other therapeutically active substances in such a way that it cannot be separated from them by simple dissolution or by other physical means*”. The August 1991 NDPSC Meeting further considered this definition, noting comments which asserted that the word “physical” was still open to interpretation. It was particularly noted that if by “physical” it was meant that a chemical reaction did not take place, then it may be possible that other separation techniques such as chromatography could be regarded as a means of physical separation. It was noted that most compounded drugs could be separated by chromatographic methods. The Committee agreed, as chromatographic methods were not simple physical means available to the ordinary householder, to vary the definition by including the word “simple” in front of “physical means” to give the current SUSDP definition:

"**Compounded**" in relation to a substance means combined with one or more other therapeutically active substances in such a way that it cannot be separated from them by dissolution or other simple physical means.

The October 2002 NDPSC Meeting, in considering the problem of pseudoephedrine diversion, agreed that certain combination products, including bilayer preparations, where pseudoephedrine could be readily separated or extracted from other components in the formulation by dissolution or other simple physical means were not included in the definition for "compounded" in the SUSDP.

At the February 2005 NDPSC Meeting the Committee noted a public submission which asserted that the most abused over-the-counter (OTC) XXXXXXXX preparation was XXXXXXXX as separating the XXXXXXXX from XXXXXXXX involved simple physical separation of the layers. The Committee agreed that this may be a formulation issue for consideration at the June 2005 NDPSC Meeting. The June 2005 NDPSC Meeting agreed to foreshadow consideration of a possible amendment to the SUSDP interpretation of "compounded" at the October 2005 NDPSC Meeting to add a statement to the effect that "compounded" does not include bilayer/multilayer preparations.

At the October 2005 NDPSC Meeting the Committee confirmed the current "compounded" definition and agreed that this definition allowed for future multilayer formulations which were not separable by simple physical means. The Committee further highlighted that current bilayer and multilayer formulations could not be considered to be "compounded" if the layers were separable by simple physical means. The Members also requested that the Secretariat confirm that all the SUSDP entries which use the definition "compounded" referred to substances with potential for abuse.

DISCUSSION

The Committee noted advice from the Secretariat that the only substances which make use of the term "compounded" within an SUSDP entry are codeine, dihydrocodeine, ethylmorphine, pholcodine and metoclopramide. The Secretariat advised that for codeine, dihydrocodeine, ethylmorphine and phocodine there appeared to be a potential for abuse as these substances were opiates. Metoclopramide, however, did not appear to be a substance with the potential for abuse.

Metoclopramide is an anti-emetic which relieves symptoms of nausea and vomiting. It works with paracetamol by increasing the contractions of the stomach and intestines, which aids in quick absorption of paracetamol. Members noted that metoclopramide was first placed in Schedule 4 at the March 1968 PSC Meeting. At the November 1999 NDPSC Meeting the Committee agreed to also include the current Schedule 3 entry:

METOCLOPRAMIDE when compounded with paracetamol in divided preparations, packed and labelled only for the treatment of nausea associated with migraine, in packs containing not more than 10 dosage units.

The Committee noted that a search of the Australian Register of Therapeutic Goods (ARTG) indicated that the majority of metoclopramide products were Schedule 4 and that there were only three products combining metoclopramide and paracetamol: XXXXXXXX, an export only product, and two domestic products: XXXXXXXX and XXXXXXXX. According to XXXXXXXX XXXXXXXX and XXXXXXXX are not multilayer formulations. The Committee also recalled that the summary of all available bi- and multilayered products listed on the ARTG presented at the October 2005 NDPSC Meeting had indicated that there were no metoclopramide products.

The Committee agreed to replace "when compounded" with "when combined" in the Schedule 3 metoclopramide entry as there did not appear to be any potential for abuse of this substance that would warrant continued restriction of the formulation to "compounded".

Members were also advised that, additionally, the definition of essential oils in the SUSDP made use of the term compounded:

"**Essential oils**" means products obtained from natural raw materials either by distillation with water or steam or from the epicarp of citrus fruits by a mechanical process, or by dry distillation. For scheduling purposes it also means:

(a) oils of equivalent composition derived through synthetic means; or

(b) compounded oils of equivalent composition comprising a mixture of synthetic and natural components.

The Committee was advised that the definition of essential oils was considered at the August and November 2000 NDPSC Meetings where the current definition was confirmed. The Minutes of these Meetings indicated that reference to compounded in part b) of the definition was never considered to mean compounded as defined in the SUSDP. The use of compounded for the essential oils definition (b) referred to an alternative meaning of compounded i.e. not a formulation usage but a preparatory usage – preparation and mixing to form the essential oil. The Members agreed that this was an inconsistency and further agreed that the wording "prepared mixtures of" should replace "compounded" in part b) of the essential oils definition as this gave a clearer and more transparent indication of what was meant by the entry.

The Committee noted a submission from XXXXXXXX supporting any clarification in the definition of the term 'compounded', noting the issues raised by the previous consideration of pseudoephedrine (see background).

DECISION 2006/46 - 22

The Committee:

- Confirmed the current definition of compounded.

- Agreed to broaden the Schedule 3 entry for metoclopramide to combination formulations with paracetamol as metoclopramide did not have the potential for abuse that would require the formulation method to be restricted to one complying with compounded.
- Agreed, for clarity, to replace "compounded" in part (b) of the essential oils definition with "prepared mixtures of".

Schedule 3 – Amendment

METOCLOPRAMIDE – amend entry to read:

METOCLOPRAMIDE when combined with paracetamol in divided preparations, packed and labelled only for the treatment of nausea associated with migraine, in packs containing not more than 10 dosage units.

Part 1 Interpretation – Amendment

Paragraph 1(1) – Amend entry for essential oils to read:

"**Essential oils**" means products obtained from natural raw materials either by distillation with water or steam or from the epicarp of citrus fruits by a mechanical process, or by dry distillation. For scheduling purposes it also means:

(a) oils of equivalent composition derived through synthetic means; or

(b) prepared mixtures of oils of equivalent composition comprising a mixture of synthetic and natural components.

11.6 PANTOPRAZOLE

PURPOSE

The Committee was advised of developments with the generation and provision of educational materials and supply protocols for pharmacists to appropriately supply S3 pantoprazole.

BACKGROUND

Pantoprazole is a proton pump inhibitor (PPI) similar to esomeprazole, omeprazole, lansoprazole, and rabeprazole. At the June 2005 Meeting, the Committee agreed to include in Schedule 3 pantoprazole in oral preparations containing 20mg or less of pantoprazole for the relief of heartburn and other symptoms of GORD in packs containing not more than 14 days supply. It was also agreed that the implementation date

for this decision would be 1 March 2006 to allow adequate time for collaboration with the pharmacy profession and the generation and provision of education materials and supply protocols for pharmacists to supply S3 pantoprazole appropriately. The Committee did not consider an Appendix H listing for pantoprazole as there was insufficient information at the time to make an informed decision.

After the June 2005 Meeting, the sponsor was written to and supplied an extract of the Edited Minutes. In that correspondence, it was pointed out that the Committee delayed the implementation date of the scheduling amendment in order to allow time for collaboration with the pharmacy profession in drafting the educational materials and supply protocols for S3 pantoprazole. The sponsor was asked to submit the final draft of these materials to the Committee in time for the October 2005 Meeting. The sponsor confirmed that while the materials were under development, they could not advise of an expected completion date, though they were anticipated to be completed by the end of the year.

At the October 2005 Meeting, the Committee agreed to vary the decision made at the June 2005 Meeting by delaying the implementation date for the rescheduling of oral pantoprazole 20mg to Schedule 3 to 1 May 2006 to allow the sponsor adequate time to develop pharmacist educational material.

DISCUSSION

The Committee noted that the sponsor was yet to provide the Secretariat with a copy of the pharmacist educational materials for pantoprazole. The sponsor had been contacted and informed the Secretariat that they were not in a position to put together the educational materials at this stage. The sponsor could not say when the educational materials would be available and asked whether it would be possible to suspend or hold the change.

The Committee reaffirmed its view that in relation to pantoprazole, it was necessary to ensure that, should a product be presented for registration, then it was essential that it be accompanied by an appropriate level of information for an S3 product.

Some Members were also concerned that should the decision be implemented prior to registration there was potential for a “broken” Schedule 4 product to be dispensed as a Schedule 3 medicine in the absence of both approved information such as CMI and PI and pharmacist educational material.

The Committee discussed options for delaying the implementation date having regard to the sponsor’s advice that it was uncertain when the pharmacist education materials would be available. Options included linking the implementation date to the time of product registration, to the usual date when State/Territories give legal effect to scheduling decisions (either by reference to the NDPSC or via their own processes) or to a date in the future thereby allowing the Committee to further amend this date should an application for registration be presented in the intervening period.

The Committee also received advice relating to the Committee's decision making procedures and the specifying of an implementation date. The advice confirmed that the Committee is able to delay the implementation date of a scheduling decision.

DECISION 2006/46 – 23

Having regard to this advice, the Committee agreed to amend the implementation date for the oral pantoprazole Schedule 3 amendment to 1 May 2008 and to include this decision in the Gazette Notice and the Record of Reasons.

Schedule 3 – New entry

PANTOPRAZOLE in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days of supply.

Schedule 4 – Amendment

PANTOPRAZOLE – amend entry to read:

PANTOPRAZOLE **except** when included in Schedule 3.

Effective date – 1 May 2008

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

12.1 SUSDP, PART 4

12.1.1 KETOTIFEN

PURPOSE

The Committee considered a proposal from XXXXXXXX to reschedule ketotifen in topical eye preparations containing 0.025% or less of ketotifen from Schedule 4 to either Schedule 3 (with Appendix H listing) or Schedule 2.

BACKGROUND

Ketotifen is an antihistamine H-1 receptor antagonist and has stabilising action on most cells. It is used in the prophylactic management of asthma and in the treatment of allergic conditions such as rhinitis.

Ketotifen was included in Schedule 4 of the SUSDP at the November 1998 NDPSC meeting as a result of consideration of scheduling proposals arising from the July 1998 TTHWP meeting.

The April 2004 ADEC meeting recommended the approval of an application by XXXXXXXX to register XXXXXXXX containing the new medicine ketotifen (present as ketotifen hydrogen fumarate) XXXXXXXX µg/ mL opthalmic solution in bottles for use in the symptomatic short-term treatment of seasonal allergic conjunctivitis (SAC) in adults and in children 3 years or older.

XXXXXXXX considered that ketotifen 0.025% eye drops met the criteria for a medicine to be included in Schedule 2 of the SUSDP, however, in view of the less then usual local marketing experience, a Schedule 3 classification (with advertising) was proposed to allow direct supervision by the pharmacist.

XXXXXXXX also noted that the possibility of abuse of ketotifen 0.025% eye drops is extremely low by virtue of its presentation in a XXXXXXXX intended for up to 4 weeks' treatment or in strips of XXXXXXXX single dose units.

DISCUSSION

The following points from the XXXXXXXX submission were noted.

- Inclusion of ketotifen 0.025% for opthalmic use would align the Australian poisons schedule with the New Zealand classification in accordance with the principles of Trans Tasman Harmonisation.
- In terms of safety, ketotifen eye drops are well tolerated and safe in all populations and age groups with no clinically significant changes in blood pressure or heart rate and no significant findings noted on visual acuity, pupil size and reactivity or slit-lamp examination. Dilated ophthalmoscopy and measurements of intra-ocular pressure have not revealed any abnormalities. Adverse events are usually mild or moderate in intensity. These include burning or stinging of the eyes, blurring of vision, dry eyes, dry mouth, skin rash, eczema, urticaria or other allergic reactions and headache and somnolence, all occurring in less than 1-2% of cases and appropriately listed in the approved PI.
- The sponsor argues, reasonably, that when used as an S3 product with guidance from the pharmacist and with adequate directions for use, this product should provide significant benefit for consumers. It is pointed out that all other products used to treat SAC are included in S2 of the SUSDP, e.g. other H1-receptor antagonists (levocabastine hydrochloride, antazoline salts and pheniramine maleate) and mast cell stabilisers (sodium cromoglycate and lodoxamide).
- Although the application for rescheduling was being made with less than two years Australian marketing experience as a prescription product, the sponsor considered this was justified and the evaluator concurred that it would still be reasonable to approve this for S3 availability as there was extensive overseas post-marketing experience, e.g. ketotifen eye drops have been available OTC in a number of Nordic countries since August 2003, including Sweden since March 2004. There are over 2 million patient-years exposure for ketotifen 0.025% and 0.05%. Oral ketotifen has not been

marketed in Australia although some experience in the ADRAC database as a result of clinical trial reports during the 1980's and ongoing supply under the SAS scheme suggest few areas for concern. Six PSUR's have been conducted and the most recent (PSUR 6) was included in the submission; there were no new safety issues identified. The majority of reported AE's related to symptoms and signs which were expected, ie ocular irritation such as itching, burning, increased tearing and conjunctival oedema, many of these also being associated with the underlying condition.

- The evaluator further agreed that this product fulfilled criteria for S3 listing. Thus, SAC is generally self-limiting over several days to months and is not life threatening. Where previously diagnosed by medical practitioners, the patient should be able to self-diagnose and self-manage symptoms (however the CMI should state that although pharmacist attention is required, medical follow up may be necessary if symptoms do not improve). There is low potential for abuse or harm from inappropriate use. Moreover the proposed daily dose is one quarter of the recommended dose of the Japanese product (0.05% qid) which has been used for over 10 years without any significant safety concerns. This agent has a wide therapeutic index; oral ingestion of the full contents of a 5 ml bottle, corresponding to 1.25 mg ketotifen, is lower than the recommended 2 mg daily dose for oral formulations and thus should not result in any significant problems.
- XXXXXXXX proposes to develop a comprehensive education and advertising campaign reinforcing the knowledge of SAC and this will include a PSA-accredited website with continuing professional education points upon completion of educational modules, direct mailing, representative calls, pharmacy journal advertising and consumer information about the product.
- The sponsor also sought to include ketotifen in Appendix H. However, consumers are already likely to have information about the easily identifiable symptoms of SAC and are familiar with the process of use of other topical therapy for this common condition as S2 items without Appendix H inclusion. Thus, it was not clear to the evaluator that this product should merit any particular advantage over other treatments by inclusion in Appendix H. Information transmission of this common condition by pharmacists and broader experience with this product should be achievable with S3 listing alone, without the need to advertise the product.

Public Submissions

The Committee noted public submissions received from XXXXXXXX, XXXXXXXX and XXXXXXXX.

XXXXXXXX

XXXXXXXX opposed the proposal. XXXXXXXX was particularly concerned that because ketotifen eye drops are not indicated to treat all the signs and symptoms of seasonal allergic conjunctivitis and are only indicated for short term use (up to 4 weeks), rescheduling would result in use outside its registered indication.

XXXXXXXX also noted that the New Zealand MCC did not support the reclassification of ketotifen eye drops from Prescription Only to a Pharmacy Medicine citing concerns about the quality of the pharmacovigilance systems in the countries where the products had already made OTC medicines. XXXXXXXX also noted that, apart from New Zealand, ketotifen eye drops were not yet available as an OTC medicine in any country. Further experience of the product was required before OTC availability.

XXXXXXXX

XXXXXXXX supported the rescheduling of ketotifen for ophthalmic use.

XXXXXXXX

XXXXXXXX did not support either option in the proposed amendment. XXXXXXXX believed that there had not been sufficient experience of the supply of ketotifen in the major OTC markets in the world to support its safety in the OTC setting.

Sponsor's Comment on Evaluator's Report

The Committee forwarded the evaluator's report to XXXXXXXX for comment. XXXXXXXX provided the following comment.

- XXXXXXXX agreed with the evaluator's recommendation that S3 listing be approved. However, XXXXXXXX disagreed with the evaluator's recommendation that Appendix H listing be rejected as this recommendation appeared to be based on an incorrect assumption that such a listing would convey an advantage on ketotifen 0.025% for ophthalmic use by allowing them to be advertised when topical S2 products for seasonal allergic conjunctivitis are not advertised.
- As advertising of S2 items is already permitted, XXXXXXXX argued that inclusion in Appendix H would not provide any advantage for this product over other treatments. Rather, advertising of ketotifen 0.025% for ophthalmic use would inform consumers of a new treatment option and prompt them to seek advice from their pharmacist on which treatment best meets their needs.
- Based on the data included in the XXXXXXXX proposal and the conclusions of the evaluator that ketotifen 0.025% for ophthalmic use should provide significant benefit for consumers, that safety and tolerability are not questioned and that there is a low potential for abuse or harm from inappropriate use, XXXXXXXX requested that S3 scheduling with Appendix H listing be approved.

The Committee noted that XXXXXXXX intended to develop advertising and education materials in cooperation with the Pharmacy profession. However, a member expressed reservations about the inclusion of ketotifen in Appendix H until those education materials had been developed. The Committee agreed that, given experience with ketotifen and other similar opthalmic preparations for the treatment of SAC, pharmacists already had appropriate expertise in this area. It was noted that the development of pharmacist education materials would reinforce what should already be known about

SAC and how ketotifen differs from other products used for this condition. It was therefore unnecessary to defer the decision in regard to inclusion into Appendix H.

DECISION 2006/46 - 24

The Committee agreed to reschedule ketotifen in topical eye preparations containing 0.025 percent or less of ketotifen from Schedule 4 to Schedule 3 on the basis the product fulfilled criteria for S3 listing. It was noted that such an approach would also result in harmonisation with New Zealand.

The Committee further agreed on the basis of potential public health benefit to include ketotifen in Appendix H of the SUSDP with the standard implementation date of 1 September 2006.

Schedule 4 – Amendment

KETOTIFEN **except** when included in Schedule 3.

Schedule 3 – New Entry

KETOTIFEN for ophthalmic use in medicines containing 0.025 per cent or less of ketotifen.

Appendix H – New Entry

Ketotifen.

12.1.2 AZELASTINE HYDROCHLORIDE

PURPOSE

The Committee considered a proposal from XXXXXXXX to reschedule azelastine in topical eye preparations containing 0.05% or less of azelastine from Schedule 4 to Schedule 2.

BACKGROUND

ADEC recommended the approval of azelastine hydrochloride XXXXXXXX mg/ml eye drops at its February 2005 meeting for the 'treatment and prevention of the symptoms of seasonal and non-seasonal (perennial) allergic conjunctivitis in adults and children 4 years and older', with subsequent approval by the TGA. The sponsor now requested that the NDPSC consider the rescheduling of this product from S4 to S2 based on evidence from overseas countries where it is available as a non-prescription product, and that a number of other ocular products registered in Australia for allergic conjunctivitis are S2 items.

Azelastine hydrochloride is an antihistamine H1 receptor antagonist initially developed as a tablet formulation for the prophylaxis and treatment of allergic rhinitis and bronchial asthma and marketed as tablets and granules in Japan since 1987 and was also available in some European countries and Korea in different strengths and dosages. An intranasal formulation was subsequently developed for seasonal and perennial allergic rhinitis; this had, since 1997, been available in the UK without prescription in adults and more recently extended to include children and perennial allergic rhinitis and was also available in the USA, Australia and New Zealand. In May 2000 the NDPSC supported the inclusion of azelastine in Schedule 4 with an exemption to S2 for preparations for nasal use.

The eye drop formulation was registered in 1998, in the EU/UK initially for seasonal allergic conjunctivitis in adults and children aged 12 years and in children aged 4 years and over from 1999. Azelastine eye drops are currently licensed in more than 50 countries worldwide including New Zealand and the US. An OTC switch from prescription only status was granted in 2002 in Denmark, and subsequently in the UK, Germany and Switzerland.

The approved dosage regimen in Australia was as follows:

- Seasonal allergic conjunctivitis: One drop in each eye twice daily. Increase if necessary to four times daily in adults and children four years and older.
- The same dosage regimen is recommended for up to six weeks for patients with non-seasonal (perennial) allergic conjunctivitis.

The sponsor pointed out that a number of other preparations for use in allergic conjunctivitis are in S2, including mast cell stabilisers (lodoxamide, sodium cromoglychate), vasoconstrictors (naphazoline hydrochloride and nitrate, xylometazoline hydrochloride) and antihistamines (levocabastine, antazoline phosphate and sulphate, and pheniramine maleate).

DISCUSSION

The company submission was assessed by an external evaluator. The evaluator noted that, whilst other available products for allergic conjunctivitis are available as S2 items, there was no local experience as yet with azelastine ocular drops, although there is international experience with this product as an OTC medication from 2002. This product did seem to fit S2 requirements. It is substantially safe in use but advice or counselling is available if necessary, is for minor ailments or symptoms which can be easily recognised by the consumer and does not require medical diagnosis or management, has low abuse potential, low potential for harm from inappropriate use, low or well characterised incidence of adverse experiences and minor interactions with commonly used substances or food, and has a wide therapeutic index and low risk of masking a serious disease.

However, an initial medical diagnosis of allergic conjunctivitis may be necessary before initiating treatment ie an S3 requirement. Furthermore, due to the absence of any local

experience, and in light of the sponsor's undertaking to provide 3 years of PSURs after Australian registration, the external evaluator suggested that an alternative approach might be to place this product in S3 initially to allow greater pharmacist and consumer familiarity with its use.

A copy of the evaluator's report was provided to XXXXXXXX. No response was received.

Public Comment

The Committee noted that public comment had been received from XXXXXXXX. XXXXXXXX did not support the proposed amendment noting that the proposed change was premature and should not be supported because there is insufficient experience in the safety of use of azelastine hydrochloride 0.05% w/v eye preparations in Australia and no experience of the use of this eye preparation in the OTC setting in other major markets.

DECISION 2006/46 - 25

The Committee concurred with the evaluator's report and agreed that, due to the absence of any local experience, and in light of the sponsor's undertaking to provide 3 years of PSURs after Australian registration, azelastine in eye preparations containing 0.05 percent or less of azelastine be included in Schedule 3 of the SUSDP, noting also the extensive experience of the use of the substance over a long time.

The Committee agreed to seek OTC Medicines Section advice on the need to limit pack size based on overseas experience of pack sizes up to 6 mls, length of treatment and also any need for any age limitation.

The Committee also agreed to include Azelastine in Appendix H of the SUSDP on the basis of public health benefit.

Schedule 3 – Amendment

AZELASTINE – amend entry to read:

AZELASTINE in topical eye preparations containing 0.05 per cent or less of azelastine.

Schedule 4 - Amendment

AZELASTINE – amend entry to read:

AZELASTINE **except** when included in Schedule 3.

Appendix H - New Entry

Azelastine

12.1.3 IBUPROFEN (400 MG TABLET)

PURPOSE

The Committee considered a proposal from XXXXXXXX to reschedule ibuprofen in divided doses, each containing 400mg, in packs of 50 or less dosage units, with a maximum daily dose of 1200mg, from Schedule 4 to Schedule 2.

BACKGROUND

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, post-operative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever.

Ibuprofen was first included in Schedule 4 of the SUSDP in February 1973. At the May 1989 meeting, ibuprofen in packs of 24 or less tablets or capsules for the relief of dysmenorrhoea or of pain associated with inflammation was rescheduled to Schedule 3. The Schedule 3 entry was amended over several meetings since and in May 1995, ibuprofen when the only therapeutically active substance in divided preparations for oral use containing 200 mg or less of ibuprofen per dosage unit in a pack containing 50 or less dosage units and labelled with a recommended daily dose of not more than 1200 mg, was rescheduled from S3 to S2.

The May and August 1998 meetings considered the proposal to exempt from scheduling ibuprofen in divided dosage units containing 200mg or less of ibuprofen per unit, in pack sizes of 24 or less. The Committee did not support this proposal at the time due to the concerns raised over potential health risks from unrestricted availability of another NSAID for use as an analgesic. At the October 2002 meeting, the Committee agreed to exempt ibuprofen for external use on the basis of the safety data reviewed at the time.

The June 2003 NDPSC Meeting, following consideration of public comment from a wide range of stakeholders groups and professional bodies and epidemiology data, agreed to exempt from scheduling, divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 25 or less dosage units when labelled with a recommended maximum daily dose of 1200 mg of ibuprofen and compliant with the mandatory label requirements. The evaluator of the applicant's submission noted in its report to the NDPSC that there was reasonable evidence to show that ibuprofen, used intermittently in low doses, was as well tolerated as paracetamol, better tolerated than aspirin and safer than paracetamol in overdose. It was therefore recommended that exempting certain low dose ibuprofen oral preparations in small pack sizes from the requirements of scheduling was unlikely to lead to any public health concerns, and that it

would provide consumers with an additional choice of simple analgesic product available at general retail outlets.

In addition, the Committee commenced a review of label requirements for non-prescription analgesics including NSAIDs in June 2003, which took several meetings to finalise, in response to the recommendations of the *Review of non-prescription analgesic – An update,* which was released by MEC in April 2003.

The October 2005 meeting also amended the S2 entry for ibuprofen to transfer the warning statements to the RASML.

DISCUSSION

Prior to the Committee's discussion of this agenda item, the Chair excused from the meeting the XXXXXXXX, who had declared a Conflict-Of-Interest.

The Committee noted that XXXXXXXX had sought reclassification from S4 to S2 of divided doses of ibuprofen 400 mg in preparations for oral use when labelled with a recommended dose of 400 mg and a daily dose not exceeding 1200 mg of ibuprofen in packs of 50 or less dosage units. XXXXXXXX raised the following points in support of its application:

- The proposed product for the treatment of adults and children aged 12 years and over satisfies the criteria for Schedule 2 classification on the grounds that:
    - The product is indicated for temporary relief of mild to moderate self-limiting pain conditions with inflammatory component and is suitable for self-selection by a consumer.
    - There is no evidence of abuse potential or diversion for illicit use.
    - There is a low potential for harm from inappropriate use. A fatal dose has not been defined. The intention is to provide the consumer with a convenient, single dosage unit format such that there is an option to take the recommended non-prescription dose of 400 mg ibuprofen as a single dosage unit rather than the usual two x 200 mg dosage units. It is not expected that the availability of 400 mg strength of ibuprofen will increase the size of the analgesic market but the new dosage strength should provide another option for consumers.
    - The few adverse effects and contraindications are well characterised when the total daily dose is limited to 1200 mg and the labelling directed consumers to seek medical advice in certain circumstances. As demonstrated in a previous research study of consumer behaviour (reviewed by NDPSC in 2003), consumers with health issues did read the labels of medicines and could determine whether a product was suitable for them. The availability of a product within the pharmacy setting ensures access to professional advice where required.
    - Ibuprofen has a wide margin of safety and ibuprofen 400 mg has a long history of safe use of more than 15 years in some countries at non-prescription level such as the UK, Italy, Denmark, Finland, Sweden and Canada. Furthermore,

ibuprofen's safety record is significantly better than other non-steroidal antiinflammatory agents (NSAIDs).

- o There is a low risk of masking serious disease, largely due to the easily recognised conditions for which non-prescription ibuprofen is indicated and to the short-term duration of use. The labelling directs consumers to seek medical advice if symptoms persist.
- Advertising and promotion will be aimed at educating the consumer as to the availability of the single tablet dose product and to use medicines strictly according to label instructions and recognise the value of professional advice where deemed to be necessary.

Members noted the evaluation report which made the following comments on the sponsor's submission taking into account the assessment factors for Schedule 2:

Suitability for self treatment of a minor ailment or symptom capable of being monitored by the consumer

- Ibuprofen, in individual doses of 200-400mg and no more than 1200mg daily, is suitable for self treatment of mild to moderate self-limiting ailments such as headache, backache, dental pain, and period pain, as listed on the proposed pack. The indications approved by the TGA are as follows:

  "The temporary relief of pain and/or inflammation associated with headache (including migraine and tension headache), dental pain, period pain, arthritis, aches and pains associated with the common cold or flu, backache, sinus, muscular and rheumatic pain. Reduces fever."

  All of these ailments are minor and are capable of being monitored by the consumer.

- The key issue noted is the size of each individual dose. The 200mg tablet preparations of XXXXXXXX that are currently unscheduled (pack size of 24) or included in Schedule 2 (pack size of 48) are labelled with the dosing instructions: "Adults and children from 12 years: 2 tablets, then 1 or 2 tablets every 4 hours as necessary (maximum 6 tablets in 24 hours)." The proposed labelling for XXXXXXXX (400mg tablets) is "Adults and children from 12 years: 1 tablet/capsule every 4-6 hours as necessary (maximum 3 tablets/capsules in 24 hours)". The option of a 200mg dose is therefore no longer possible and this reduces the suitability of the product for the self treatment of a minor ailment that may only require a dose of 200mg.

Extremely low abuse potential

- Ibuprofen is not a drug of abuse in any dosing form, including tablets for oral use. There is no likelihood of diversion for illicit use.

Low potential for harm from inappropriate use

- Ibuprofen has a very wide therapeutic index and a potentially fatal dose has not been defined in humans. A report of an adolescent who ingested 100 grams (100,000 mg) of ibuprofen indicates that, although significant toxicity ensued (including coma, metabolic acidosis and mild thrombocytopenia), there was no renal dysfunction or GI

bleeding. The patient recovered within 3 days with supportive management and had no medical sequelae (Seifert et al 2000; ref 2 in submission).

Low or well characterised incidence of adverse effects or side effects and contra-indications for which advice or counselling is available

- The submission provided adverse drug reaction reports from the global database for XXXXXXXX and ADRAC reports for ibuprofen in S2 and S4 products in Australia. The reporting rate of ADRs was very low in both Australia and the UK, and the latter did not demonstrate a disproportionate rise in 1994 when general sales were approved in the UK (which accounts for about 30% of the market). The UK database contains 929 reports by 539 patients, on a background of sales of nearly 10 billion adult doses over the same period. The ADRAC database contains 170 reports for XXXXXXXX over the period 1972 to 2005. The overall conclusion that ibuprofen is a safe OTC product is reasonable.

- The submission also referred to the PAIN study (Moore et al 1999; supplied as reference 4), a large randomised clinical trial of the tolerability of aspirin, ibuprofen and paracetamol for short term analgesia (up to 7 days of treatment) carried out in 8,677 adult subjects in general practice. The results indicated that ibuprofen was tolerated as well as paracetamol and significantly better than aspirin, the rates of significant adverse events being: aspirin 18.7%, ibuprofen 13.7% and paracetamol 14.5%. Gastrointestinal adverse effects were no higher for ibuprofen than for paracetamol. Ibuprofen was generally accepted as the least gastro-toxic of the non-steroidal anti-inflammatory agents (Hersh et al 2000).

- The labelling carries appropriate warnings against use by persons for whom ibuprofen is contraindicated. The safety record of low dose ibuprofen used in the OTC setting is excellent.

- Only minor or well characterised interactions with commonly used substances or food for which advice or counselling is available.

- Interactions with other drugs are unlikely to occur at the recommended dose and duration of dosing of XXXXXXXX when provided in small pack sizes, provided consumers do not use the drug chronically. Prolonged usage leads to the potential hazard of interactions with angiotensin converting enzyme inhibitors (to cause renal dysfunction), antihypertensives and antifailure drugs (lack of efficacy), and anti-platelet drugs or anticoagulants (increased risk of GI bleeding).

A wide therapeutic index

- Ibuprofen administered orally had been demonstrated to have a wide therapeutic index, with an effective dose for mild-moderate pain being 200-400mg, and the toxic dose being very high in relation to serious toxicity. The previously mentioned case report of an adolescent who made an uneventful recovery after ingestion of 100 grams of ibuprofen illustrated this.

Low risk of masking a serious disease

- Given the indications for low dose oral ibuprofen, the risk of masking a serious disease is very low.

Low risk of compromising medical management of a disease

- Assuming that consumers adhere to the directions for use and in particular the warnings provided, there is a low risk of compromising medical management of a disease. In antiinflammatory doses, NSAIDs including ibuprofen could promote sodium and fluid retention and thus exacerbate conditions such as congestive heart failure and hypertension, but this would be unlikely to occur at the low total daily doses allowed for OTC use. The proposed maximum daily dose is unlikely to mask severe pain originating from serious causes.

Safety in use with counselling by a pharmacist available if required

- This is a key issue in this application. It could be argued that, given that the lower end of the effective dose range (200-400mg) could not be achieved with this product, it should only be used by individuals who require a 400mg dose, either because they have severe symptoms or because they have failed to respond to 200mg. The selection of a 400mg unit dose product rather than a 200mg unit dose product may therefore be a decision that would be better made with pharmacist advice and counselling than without it.

Public health considerations

- In relation to the unit dose, the major concern is that consumers will be forced to take 400mg when 200mg may have been effective. There is good evidence in the literature from placebo-controlled trials that ibuprofen in a 200mg dose is effective in the management of migraine (Codispoti et al 2001), mild to moderate headache (Nebe et al 1995), tension headache (van Gerven et al 1996) and symptoms of colds and flu (Grebe et al 2003). A review of OTC analgesics concluded that a single dose of 200mg of ibuprofen was roughly equivalent in analgesic efficacy to 650-1000mg of aspirin or paracetamol, while the proposed dose of 400mg was significantly more efficacious than these older drugs (Hersh et al 2000). Hersh et al (2000) also concluded that a clear dose-response relationship had been demonstrated between 200mg and 400mg of ibuprofen in postsurgical dental pain models.

- In the migraine trial (Codispoti et al 2001), ibuprofen 400mg was not superior to 200mg except in cases with severe baseline pain intensity, in whom the 400mg dose was significantly superior to placebo while 200mg was not. While it is unlikely that short-term use at a maximum daily dose of 1200mg would lead to significant problems, a fundamental principle of therapeutics, particularly in relation to over-the-counter treatment, is to expose an individual to the minimum effective dose. Thus there appears to be a place for XXXXXXXX 400mg tablets in consumers with severe pain, but the use of this product would potentially result in overtreatment of many others who would have responded adequately to a 200mg dose. The Sponsor had not provided a convincing argument to support the implication that a 400mg unit dose would be appropriate for all consumers purchasing this product. The argument that a single unit dose is likely to improve compliance is relevant only if 400mg is the appropriate dose in the circumstances. It could be argued that requiring pharmacist advice may be appropriate to assist consumers in making the correct choice of preparation for their needs, and therefore that a Schedule 3 classification may be more appropriate.

Recommendation

- The submission argues that a pack of 50 x 400mg dosage units of ibuprofen should have the same scheduling as a pack of 100 x 200mg dosage units when both are labelled with a maximum daily dose of 1200mg. While the logic of this is clear, and it is very unlikely that any significant hazard would result from the availability of the 400mg product without prescription, it is also likely that the ready availability of this product would lead to a greater use of the maximum dose (400mg) in consumers in whom a 200mg dose would have been effective. The usual dosage recommendation is 200-400mg three times daily, and there is good evidence for a dose-response relationship for ibuprofen and that many minor conditions for which ibuprofen is appropriate treatment will respond adequately to a 200mg dose. For this reason, it is recommended that the 400mg unit dose product be down scheduled to Schedule 3, so that consumers can receive advice from pharmacists and use this product only when they have severe pain likely to require a 400mg dose.

The Committee noted that the evaluator's report was provided to the sponsor for comment. In response to the evaluation report's recommendation, the applicant raised a number of points including the following:

- The S2 entries for aspirin and paracetamol currently have a total pack size limit and have no dosage unit restriction. Furthermore, the specific exclusions provided for in the Schedule 2 entry for paracetamol allow for the availability of unscheduled paracetamol preparations that are not restricted to the minimum recommended dose. The same approach to the unit dose should also be applicable to the proposed rescheduling of 400 mg ibuprofen.
- The 400 mg ibuprofen tablet has a long history of safe use from as early as 1984. There was no evidence to suggest that the availability of 400 mg ibuprofen without prescription increased adverse events or causes any consumer confusion.
- Further consideration as to the interpretation of the recommended dosage regimen for non-prescription ibuprofen may serve to alleviate the concerns expressed in the evaluation report with regard to a 400 mg unit dose. The report states that for ibuprofen "the usual recommended dose for minor indications is 200-400mg up to three times daily" however, this does not entirely reflect the approved recommended dosage instructions for XXXXXXXX 200 mg ibuprofen, which is 2 dosage units (i.e. 400 mg) then 1 or 2 dosage units every 4 hours as necessary with a maximum of 6 dosage units in 24 hours (i.e. 1200 mg). The key dosage recommendations are that:

  each individual ibuprofen dose does not exceed 400 mg; and
  the total maximum daily ibuprofen dose does not exceed 1200 mg, as stipulated in the current Schedule 2 entry.

- The interpretation by XXXXXXXX of the intention of the recommended dose of non-prescription ibuprofen varies from that which is reflected in the evaluation report. The appropriate limits relate to the maximum individual dose and the total maximum daily dose, rather than the minimum unit dose. Speculation that the down scheduling

to Schedule 2 of ibuprofen in a 400 mg unit dose is likely to lead to greater usage of the 400 mg dose is baseless. Where flexibility of dosing is required (for example, in children), liquid ibuprofen and 200 mg solid dose preparations will still be available.

- XXXXXXXX does not dispute that there exists a dose response for ibuprofen, and that studies, including those referenced in the evaluation report, do demonstrate that 200 mg ibuprofen is more effective than placebo in providing analgesia. However, this does not negate the suitability of the inclusion of 400 mg ibuprofen in Schedule 2. Codispoti et al (2001) state that their data suggests "little benefit of ibuprofen at doses of more than 400 mg for the treatment of migraine headache". Beaver (2003) reviews the analgesic efficacy of ibuprofen, and concludes from the Codispoti study that 400 mg ibuprofen "has been shown to be superior to a 200 mg dose in patients with migraine headache". Beaver also refers to the study by Schachtel et al (1996) that demonstrates that 400 mg ibuprofen is superior to paracetamol 1000 mg in relieving tension headache, also an approved non-prescription indication for ibuprofen.
- Determination of appropriate product indications is also the role of the TGA, rather than the NDPSC. Whilst the proposed rescheduling application of 400 mg ibuprofen proposes identical indications to those already approved for non-prescription ibuprofen, the suggested indication provided in the evaluation report is for "severe" pain. No clarification is provided as to what indications are considered to constitute severe pain. However, it is assumed that this would be significantly different to those indications currently approved for non-prescription ibuprofen, which are considered to be mild to moderate in nature. In any case, it would be doubtful as to whether 1200 mg ibuprofen per day would provide appropriate analgesia for "severe" pain states. There exists an ibuprofen-codeine combination product in the XXXXXXXX that is currently marketed and is indicated for "strong" pain (rather than "severe" pain) i.e. XXXXXXXX.
- In summary, the proposal to reclassify 400 mg ibuprofen as Schedule 2 only includes currently approved non-prescription indications for ibuprofen, with a consistent dosage regimen to that of 200 mg ibuprofen, i.e. an individual dose no greater than 400 mg and a maximum total daily dose not exceeding 1200 mg ibuprofen. Furthermore, entry into Schedule 2 would still provide the consumer with the opportunity to seek advice or counseling from the pharmacist if required. Given this, there would seem to be no rationale for a recommendation of Schedule 3 for this application and XXXXXXXX maintains that the most appropriate entry for this proposal is Schedule 2.

The Committee noted that the sponsor also advised that the proposed product name was modified to XXXXXXXX based on research which showed that consumers could clearly differentiate this product from existing XXXXXXXX 200 mg ibuprofen, and understand that only one dosage unit (in comparison with up to 2 for XXXXXXXX 200 mg ibuprofen) should be taken each time. It was also advised that the evaluation of this label change by the TGA was nearing completion.

The Committee noted the following points raised in the public submissions received:

- XXXXXXXX supported the proposal to include 400 mg ibuprofen in S2 on the grounds of ibuprofen's better safety profile compared to paracetamol and aspirin at OTC doses and the fact that the current dosage recommendation allowed for the administration of 400 mg of ibuprofen. XXXXXXXX supported the S2 availability of the product when indicated for the temporary treatment of headache, fever, arthritis, period pain, dental pain, common cold and acute pain where inflammation is present and when labeled with a recommended daily dose of not more than 1200 mg of ibuprofen.
- XXXXXXXX supported the retention of the current S4 status for ibuprofen 400 mg as this offered the most appropriate balance whilst preventing consumer confusion when this medicine appeared on a pharmacy shelf with the lower strength 200 mg tablets already available. The availability of 200 mg and 400 mg ibuprofen for self-selection and without pharmacist intervention at the point-of-sale could lead to overdosing and potentially result in adverse events including severe GI events. Furthermore, it was pointed out that the proposal to include the proposed product in S2 effectively allows prescription strength tablets in large pack sizes to be available without any healthcare professional intervention and was not consistent with the principle of lower dose strength and smaller pack size in less restrictive schedules.
- XXXXXXXX supported the inclusion of all OTC solid dose form ibuprofen products in S3.

The issues raised in the XXXXXXXX submission related mainly to adverse effects of NSAIDs as a class when taken for prolonged periods or on a regular basis and/or at doses greater than the current Australian OTC dose level of 1200 mg daily. The Committee noted the following issues:

- The XXXXXXXX did not adequately address the proposal to include the 400 mg per unit dose formulation in S2 based on the scheduling criteria.
- The sponsor's submission also discussed the outcome of the reviews undertaken by regulatory agencies around the world on COX-2 inhibitors and other NSAID medications in relation to their potential to cause increased cardiovascular risks. Members noted that the US Federal Drug Administration (FDA) concluded that there was no evidence that NSAIDs taken at non-prescription doses and durations increased the risk of heart attack or stroke and that the cardiovascular risk associated with short-term intermittent use of low doses of NSAIDs was very small, if any, in the absence of a predisposing condition (e.g. coronary disease). The UK's Committee on Safety of Medicines (CSM) also reviewed all the available safety data relating to non-selective NSAIDs including ibuprofen, diclofenac and naproxen. The CSM concluded that the evidence reviewed was insufficient to change the balance of risks and benefits of NSAIDs, and no changes to current prescribing practice was recommended on the basis of current evidence on thrombotic risk. In relation to non-prescription ibuprofen, CSM specifically concluded that at doses in OTC medicines (i.e. 1200 mg/day), ibuprofen has an excellent safety record, particularly in respect of

GI adverse effects and increased cardiovascular risk from short term use of low dose OTC ibuprofen was unlikely to be associated with any measurable increased risk.

- The evaluator made a valid point in that there was good evidence to suggest that 200 mg ibuprofen per dose could be effective for mild-moderate pain states and that the 400 mg /dose unit removed the option of taking the lowest effective dose. In addition, evidence was available to support a clear dose-response relationship between 200mg and 400mg of ibuprofen in post-surgical dental pain models.
- The Committee concurred with the evaluator's view that an S2 availability of the proposed product could lead to greater use of the maximum dose (400mg) in consumers in whom a 200mg dose would have been effective. Members felt that consumers should be encouraged to use the lowest effective dose of ibuprofen.

DECISION 2006/46 - 26

The Committee agreed to include 400 mg ibuprofen per dose unit in packs of not more than 50 dose units and labelled not for the treatment of children aged less than 12 years in Schedule 3 of the SUSDP. Whilst the Committee remained reassured of the safety of OTC low dose ibuprofen in small pack sizes when taken as directed, members considered pharmacist involvement at the point-of-sale essential to minimise consumer confusion over the increased strength per dose unit of the proposed product and ensure appropriate use.

The Committee also considered the inclusion of ibuprofen 400 mg in Appendix H. However, members did not support the Appendix H listing for this product on the basis that there was insufficient evidence to support the public health benefits of direct-to-consumer advertising of high dose ibuprofen.

Schedule 4 - Amendment

IBUPROFEN **except:**

(a) when included in or expressly excluded from Schedule 2 or 3; or

(b) in preparations for dermal use.

Schedule 3 – New entry

IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen, in packs of not more than 50 dosage units and labelled not for the treatment of children under 12 years of age **except** when included in or expressly excluded from Schedule 2.

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. Clotrimazole was registered in Australia for several indications, including topical vaginal use for the treatment of vaginal candidiasis.

The August 1977 NDPSC 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 in SUSDP 20. 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 XXXXXXXX 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.

DISCUSSION

The Committee noted that a submission from XXXXXXXX had been received requesting a rescheduling of clotrimazole from Schedule 3 to Schedule 2 in vaginal preparations. XXXXXXXX submission asserted that:

- Vaginal candidiasis was a common condition previously determined to be suitable for OTC treatment (occurring at least once in about 75% of women of child bearing age, and twice in about 40-50%).
- The Schedule 2 availability of clotrimazole preparations would offer easy accessibility to patients with less embarrassment, which may result in earlier treatment. XXXXXXXX asserted that research indicated that the majority of women would welcome easier access to relief of their symptoms than they currently have through pharmacies.

XXXXXXXX submission was assessed by an external evaluator. The Committee noted that the evaluation report for the XXXXXXXX submission recommended that the down scheduling application be rejected, primarily because of the unreliability of self-diagnosis of the condition and the likely impact of down scheduling on increasing both overall and inappropriate usage.

The Members considered the following matters from the evaluation report:

Safety

- Clotrimazole had been shown to be effective and safe in the treatment of vaginal candidiasis, with a response rate of about 80% in patients who have the disease.
- Clotrimazole had:
    - an extremely low abuse potential, a low potential for harm from inappropriate use and a low, well characterised incidence of adverse effects or side effects.
    - a low rate of absorption, together with rapid metabolism, resulting in low systemic exposure during topical treatment.
    - a low risk of significantly affecting the outcome of a potentially serious condition, given that users were instructed to seek medical advice if their condition failed to respond to the product within four days. The labelling also included appropriate warnings about symptoms that should provoke immediate medical attention.
    - a low risk of masking a serious disease. However, there was a risk of delaying the diagnosis of an infection that was either due to a resistant *Candida* species or to a different organism. There was also a possibility of misdiagnosis of vulvovaginitis in a patient with another urogenital condition.

Increased Usage

- The sponsor argued that vaginal candidiasis had previously been determined to be suitable for OTC treatment, and that there was no advantage in requiring pharmacist advice to users in the choice to purchase the medication. While this was a reasonable argument, down scheduling to Schedule 2 would lead to readier access for women reluctant to discuss their symptoms with a pharmacist, and could increase overall use (including inappropriate use) of these preparations.
- There was controversy in the literature about the benefit/risk ratio of increasing the ease of availability of vaginal preparations of clotrimazole and related compounds, particularly related to the unreliability of self-diagnosis of this condition due to the lack of specificity of symptoms, even in women with past experience of vaginal candidiasis.
- The likely impact of a change in scheduling from Schedule 3 to Schedule 2 was uncertain.

Unreliability of Self-Diagnosis

- There are many causes of vulvovaginitis, and the constellation of symptoms that occur with candidiasis was not specific for this condition. Self-diagnosis of the condition, with or without a pharmacist's advice and regardless of information in package inserts, was unreliable to the extent that only about one third of women self-diagnosing with candidiasis actually had the condition (according to a study by Ferris). Definitive diagnosis required laboratory investigations initiated by a medical practitioner.

Inappropriate Use

- Exposure of two thirds of users to potential adverse effects without any prospect of benefit, because they do not have the condition, was undesirable. However, vaginal candidiasis had been accepted as an appropriate ailment for a number of substances in Schedule 3, and it was clear that laboratory testing was not carried out routinely in practice, particularly in women having recurrent episodes who are familiar with the symptoms.
- The packaging and labelling were well-designed and provide adequate information for women to maximize their likelihood of appropriate use. However, the evaluation report asserted that it had been shown that reading the package insert did not improve diagnostic accuracy, mainly because the symptoms were so non-specific.
- If down scheduling from Schedule 3 to Schedule 2 resulted in greater overall usage, it would also lead to greater inappropriate usage, with the attendant costs in terms of economics and exposure to potential adverse effects.
- The use of vaginal preparations of clotrimazole could be regarded as a "diagnostic trial" identifying those women with candidiasis which could lead to fewer visits to medical practitioners; this argument assumed that this outcome outweighed the potential costs in terms of overuse of the preparations in people for whom they are not indicated.

Restriction to Recurrent Candidiasis

- The products were labelled to restrict their use to women who have previously had an episode of candidiasis, are over 18 years and have not had 2 or more infections within 6 months. Women having their first episode or frequent recurrences were advised to consult a doctor, and this was appropriate.
- Restriction of the use to those women with a previous diagnosis of vaginal candidiasis was attempted through the labelling and information provided, but the need for women with their first episode to seek medical advice was not reflected in the proposed wording of the Schedule, and it was unclear how this could be achieved.

Consideration of Scheduling of Other Azole Therapies

- Given the very similar safety and efficacy profiles of similar imidazole vaginal preparations (e.g. miconazole, econazole), it would seem logical to have all of these included in the same Schedule.

Conclusions

- Since it was unlikely that discussion with a pharmacist would improve the diagnostic accuracy of this condition, there seemed little risk associated with further deregulation to Schedule 2.
- If appropriately self-diagnosed, uncomplicated vaginal candidiasis responds very rapidly and with a high cure rate to topical antifungals such as clotrimazole. Failure

to respond would be expected to be a strong stimulus for the woman to seek medical advice within a few days.

- The toxicity and safety are established, the risks are low and benefits are potentially great (aside from the problem with misdiagnosis), and the potential hazards are small. In particular, there have been no reports of development of secondary resistance to clotrimazole. Safety in use was likely to be high with or without pharmacist involvement.
- However, the need for Schedule 2 access to clotrimazole vaginal preparations had not been clearly demonstrated with the exception of the issue of saving patients' embarrassment. It was not clear that a down-scheduling from Schedule 3 to Schedule 2 would result in the more rapid availability of products unless women are dissuaded from accessing these products because of the need to discuss their symptoms with a pharmacist. Although no evidence was provided on this point, it did seem a reasonable assumption.

The Committee noted that XXXXXXXX, in pre-meeting comment on the evaluation report, asserted that the basis of the evaluation report's objections - the potential for overall increased or inappropriate usage of clotrimazole if reclassified to Schedule 2 and the unreliability of self-diagnosis for vaginal candidiasis - were unsubstantiated. XXXXXXXX presented a rebuttal of various comments in the evaluation report, including:

Safety Profile of Clotrimazole

- XXXXXXXX asserted that the comment in the evaluation report that inappropriate use/inaccurate self diagnosis may unnecessarily expose the patient to undesirable effects should be considered in the overall benefit/risk assessment of clotrimazole.

Increased Usage

- XXXXXXXX consider that down-scheduling would facilitate readier access (this being the prime rationale for application), but did not necessarily accept the argument that use of vaginal preparations in the treatment of candidiasis would increase appreciably as a result.
- The symptoms of *Candidiasis* were distressing and caused considerable discomfort. In the majority of cases women experiencing the symptoms would seek some sort of therapy for rapid relief and thus the incidence of untreated candidiasis was likely to be small.

Unreliability of Self-Diagnosis

- XXXXXXXX asserted that the evaluation report acknowledged that candidiasis would appear to fall into the category 'Suitable for self treatment of a minor ailment or symptom capable of being monitored by the consumer' as it could be 'identified relatively reliably by the consumer if she has had previous experience of the condition, and was unlikely to be verifiable by the pharmacist'. However, in the same

paragraph the evaluator suggested that 'self diagnosis of initial and second episodes had been shown to be unreliable'.

Inappropriate Use

- The evaluator commented that the rationale and justification provided by XXXXXXXX in the application broadly addressed the Schedule 2 criteria. Given the current state of knowledge and the acceptance of clotrimazole in the Australian community as an OTC medicine for over a decade, XXXXXXXX asserted that the objection that down scheduling will lead to increased inappropriate use appeared to be baseless.
- As vaginal fungal infections could only be definitively diagnosed by culture and medical examination, close pharmacist management/counselling was not required for most occasions. Having clotrimazole currently listed as a Schedule 3 medicine did not obviate the need for a patient to seek medical examination and vaginal microbiological testing in the event of uncertain diagnosis. This situation did not change with the medicine as a Schedule 2 product.
- In the case of women who have previously experienced candidiasis, involving the pharmacist on every occasion was unnecessary. For first time sufferers the proposed labelling clearly directed consultation with the healthcare professional for diagnosis prior to use. In reality a doctor would often not make a definitive diagnosis either, opting for a simpler, less expensive and less invasive, 'treat and see' approach. In addition the package insert not only lists risk factors and symptoms that were suggestive of candidiasis, but also symptoms that were not indicative of candidiasis and cases where immediate presentation to a doctor was warranted. This limited the potential for inappropriate use.
- Discussing uro-genital symptoms could cause embarrassment for the woman and on some occasions on the part of the pharmacist, particularly if male. The lack of privacy at the pharmacy counter could make this situation worse.
- XXXXXXXX proposed labelling gives direction to women with symptoms and reinforces this information and provides differential diagnosis via the package insert.

Restriction to Recurrent Candidiasis

- The evaluation report noted that clotrimazole was labelled as recommended for use in women who have previously experienced vaginal candidiasis and that XXXXXXXX had "not reflected this in the proposed wording of the Schedule". XXXXXXXX asserted that it should be noted that Appendix F of the SUSDP required labelling that stated "seek medical advice before first course of treatment". XXXXXXXX proposed to retain this warning statement. It was not practical to restrict clotrimazole to non-first time users via the Schedule 2 entry.

Consideration of Scheduling for Other Azole Therapies

- The safety profile of other imidazole vaginal preparations were not wholly similar to clotrimazole as outlined in the submission. The pharmacokinetics and systemic

absorption via the vaginal mucosa were likely to be different and miconazole had been reported to cross the placenta whereas clotrimazole had not. Furthermore the Australian experience of the use of other imidazole medicines was not as extensive.

- The clotrimazole application should not be delayed whilst the Committee sought data for the other topical antifungals, when XXXXXXXX has provided the appropriate data to support a rescheduling application for clotrimazole that addressed the Schedule 2 criteria.

Additionally, Members were advised that XXXXXXXX had contended the evaluation report's use of a study by Ferris as grounds to support the self diagnosis concerns. XXXXXXXX provided this paper to the Committee along with a request that Members make their own independent assessment of the paper. XXXXXXXX analysis of the Ferris paper included the following:

- The study was undertaken in the US. OTC medicines in the US can be sold in large pharmacy/grocery stores where pharmacist advice is not generally available. XXXXXXXX asserted that this was clearly different to the Australian context.
- Subjects were eligible for recruitment into the study if they had symptoms which prompted them to buy an anti-fungal product and intended to use the product immediately. Subjects who had been diagnosed as having vaginal candidiasis by a health care provider were excluded.
- XXXXXXXX asserted that the study failed to identify or quantify the relationship between those recruited versus those considered ineligible to participate and those who simply declined to enrol. XXXXXXXX considered that this small study (104 women) was significantly marred by selection bias, attracting only patients who were perhaps unsure of their self-diagnosis and were prepared to undergo invasive and time consuming procedures for confirmation.
- XXXXXXXX further asserted that whilst only 34% of the subjects were confirmed as having uncomplicated *Candida albicans* a further 19% of subjects were medically diagnosed as having a mixed diagnosis of bacterial vaginosis and vulvovaginal candidiasis. This meant a total of 53% had confirmed evidence of *Candida albicans*. It was therefore likely that over half of the self selected group would have benefited from the over the counter antifungal treatment purchased.
- XXXXXXXX asserted that the papers sub analysis of patient leaflets did not appear to correspond with Australian wisdom on performance based labelling that highlights the value of the package insert in risk management and ensuring the safe and effective use of the product which is endorsed by TGA and both XXXXXXXX and XXXXXXXX.

The Committee noted a submission from XXXXXXXX expressed an interest in this issue as it had a Schedule 3 product for the treatment of vaginal candidiasis containing XXXXXXXX. XXXXXXXX reiterated the XXXXXXXX submission's arguments about the issue of self-diagnosis and asserted that it would seem reasonable that if clotrimazole was recommended for inclusion in Schedule 2 for vaginal use, then

consideration should also be given to reviewing the scheduling of the entire class of azole antifungal drugs, including XXXXXXXX, for the treatment of vaginal candidiasis.

The Committee noted that the safety and efficacy of clotrimazole had been established and were not in question.

The Committee considered the issue of the reliability of self-diagnosis, and relatedly, the reliability of pharmacist diagnosis. Members agreed that definitive diagnosis would require laboratory investigations initiated by a medical practitioner, although it was noted that often a doctor would not pursue this diagnosis method, opting for a 'treat and see' approach. A Member noted that in deciding on the Schedule 4 to Schedule 3 down-scheduling at the April 1994 NDPSC Meeting the Committee was comfortable that although there would not be an overt diagnosis in the pharmacy setting, failure to respond (because of misdiagnosis) would normally be a strong stimulus for the woman to seek advice from the pharmacist or a doctor. The Members confirmed continued Committee support for this argument.

The Committee noted that both the evaluator and the applicant had successfully argued that there was little risk of clotrimazole masking another serious condition when the clotrimazole treatment failed to treat the symptoms, for the reasons above. However, a Member asserted, and the Committee agreed, that the main reason for maintaining mandatory pharmacist involvement in the sale of clotrimazole was the alternative situation, the potential for masking another serious condition where clotrimazole had been successful in treating the symptoms. The Committee considered that:

- If clotrimazole was Schedule 2 there would be no trigger for the pharmacist to consider intervention where a woman had been successfully using clotrimazole to treat the symptoms of candidiasis, but had recurring episodes because of a serious underlying condition such as diabetes.
- The current product labelling indicated that women having frequent recurrences (i.e. 2 or more episodes within 6 months) were advised to consult a doctor. While the Members agreed that this was appropriate the Committee also noted that a patient who had been successfully treating symptoms would often not heed such labelling.
- Indeed, the embarrassment associated with discussing the condition, as identified by the XXXXXXXX submission, would inhibit some women from approaching pharmacists in this situation if the pharmacist were not required to be involved in ongoing purchases.

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 of repeated clotrimazole use masking an underlying serious condition.

12.1.5 CODEINE – CONSIDERATION OF THE SCHEDULING OF LIQUID PREPARATIONS CONTAINING CODEINE AS A SINGLE ACTIVE INGREDIENT

PURPOSE

The Committee considered the scheduling of codeine linctus.

BACKGROUND

Australia is a signatory to the *United Nations Single Convention on Narcotic Drugs, 1961* (the Convention) (available at http://www.unodc.org/pdf/convention_1961_en.pdf) and, as a signatory, has a number of obligations including to give effect to and carry out the Convention's provisions within its own territory.

One of the Convention's provisions is the list of narcotic drugs under international control (available at http://www.incb.org/pdf/e/list/yellow.pdf). Part 1, Section 2 of this list includes preparations of narcotic drugs included in Schedule II of the 1961 Convention (equivalent to Schedule 8 of the SUSDP) while Part 2 includes preparations of narcotic drugs exempted from some provisions and which are included in Schedule III (equivalent to Schedule 2, 3 or 4 of the SUSDP) of the 1961 Convention. The first item in Part 2 includes preparations of a number of substances, including codeine "*when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations*".

Where the above exemption does not apply codeine preparations are subject to Schedule II of the Convention. Thus, as per the intention of the Convention (which bases its exemption less on the potential for harm to an individual and more on the potential for illicit diversion) all single (active) ingredient undivided preparations of codeine are not exempted from any provision of the Convention.

At the February 1968 and November 1969 Poisons Scheduling Committee (PSC) Meetings, a proposal was considered to include a Schedule 4 entry for codeine along the lines set out in the above exemption from Schedule II of the Convention. The Committee agreed that phrasing of this exemption to be placed word for word into the Schedule 4 entries for all of the opiates that were available in Australia at the time. These included codeine, dihydrocodeine, ethylmorphine and pholcodine. Besides some minor editorial changes (replacing the "and" with an "or" between divided and undivided preparations at the May 1977 PSC Meeting), this format remains for the current dihydrocodeine, ethylmorphine and pholcodine Schedule 4 entries.

In the case of codeine, the Schedule 4 entry was re-worded at the August and November 1979 Meeting to introduce a more stringent specification of the amount of codeine allowable per dosage unit (from an upper limit of 2.5 % to 1%). The recommendation

was adopted at the March 1980 Meeting to give the current wording for the Schedule 4 codeine entry.

The Committee also introduced a Schedule 2 entry and a Schedule 3 entry for codeine, the wording of which evolved over time, but which consistently required the codeine to be compounded with one or more other therapeutically active substances.

The Minutes for the November 1984 DPSSC Meeting indicate that the Committee had noted that some States were experiencing problems with codeine linctus [Secretariat note: at this Meeting codeine linctus was considered to be a compounded liquid and thus Schedule 2 by the scheduling limits at the time].

At the August 1991 DPSSC Meeting the Committee considered correspondence from the Australian Register of Therapeutic Goods (ARTG) relating to the interpretation of schedule classification for codeine linctus whose formulation contained no other therapeutically active substances and were in effect a simple syrup of codeine. The Members agreed that codeine linctus preparations were Schedule 8 products. However, because of wider legal implications for the States/Territories the question of interpretation of the schedule classification, along with the existence of a definition for "compounded" (a decision of the August 1991 DPSSC Meeting), was referred to the NCCTG. XXXXXXXX.

At the May 1998 NDPSC Meeting the Committee considered interpretation of "compounded" and "therapeutically active substance" as they related to the various codeine (and dihydrocodeine) schedule entries. The Members noted that this arose because "therapeutically active" was not defined, and that there was a grey area for some substances (e.g. sucrose or glycerol). A Member suggest that one option would be to re-examine products in the marketplace with a view to removing the phrase "other therapeutically active substances" from schedule entries and replacing it with a specific list of acceptable combinations. Members agreed that although this issue needed to be resolved, it was not urgent and a paper exploring the above option could be prepared for consideration at a future Meeting. It appears that no further action was taken.

DISCUSSION

The XXXXXXXX Member requested that the Committee consider the issue of codeine linctus at the February 2006 NDPSC Meeting. This issue arose from a series of discussions initiated by XXXXXXXX. In particular, Members noted the following issues and actions:

XXXXXXXX:

- indicated that a local pharmacist had alleged that several people had recently presented to him attempting to purchase codeine linctus. When asked for the script they indicated another pharmacist in town was selling it without the need for a script. The product was labelled as a restricted drug.

- noted that codeine linctus, according to E-MIMS, was Schedule 4 (with 2 manufacturers).
- also noted that codeine linctus is a single active ingredient product (codeine 5 mg/ml) and asserted that their interpretation of the SUSDP indicated that this meant it should be a Schedule 8 product.
- requested clarification on whether codeine linctus was meant to be Schedule 4 and if so, was the wording of the Schedule 4 entry incorrect, or was codeine linctus a Schedule 8 product as it is a single active ingredient product.

XXXXXXXX:

- initially indicated that it may be Schedule 4 as, along with codeine, the product also contains methyl hydroxybenzoate. Following an exchange with XXXXXXXX it was agreed that methyl hydroxybenzoate, a preservative, was not a therapeutically active substance and as such codeine linctus was a Schedule 8 product.
- following discussions with the Secretariat, XXXXXXXX agreed that, as a single active product codeine linctus is Schedule 8, "despite their being registered and labelled as Schedule 4 and having information in MIMs that they're Schedule 4".
- noted that it appeared that these types of products were grandfathered when the TGA came into being, and nobody had picked up the discrepancy until this time.
- noted that liquid preparations containing codeine as a single active ingredient have been on the market and available for many years as Schedule 4's, and there appears to be little evidence of information that these products have been the subject of abuse or diversion.

The Secretariat:

- confirmed that there does not appear to be a punctuation error or oversight in the current Schedule 4 entry for codeine.
- contacted the appropriate unit in the Drug Safety and Evaluation Branch (DSEB) of the TGA suggesting that they review the PI and CMI for liquid preparations containing codeine as a single active ingredient to remove any ambiguity about these preparations being Schedule 8.

The Committee also noted that a historical concern with the availability of codeine containing preparations was diversion for the manufacture of heroin.

Advice was received from XXXXXXXX in relation to the scheduling of single active liquid preparations of codeine. This advice reiterated the background information regarding the Convention including that single active liquid preparations of codeine would be included under Schedule II of the Convention. XXXXXXXX also indicated:

- As part of the Department of Health and Ageing's reporting requirements under the Convention, annual reporting to the United Nations' International Narcotics Control Board (INCB) is required in respect of the quantities of codeine consumed for

medical and scientific use in respect of both controlled and uncontrolled preparations (Schedules II and III of the Convention, respectively).

- Currently, the OCS assembles annual consumption figures for substances included in Schedule II from weekly reports of domestic consumption of raw materials and finished goods included in Schedule 8 that are provided by licensed companies in accord with State/Territory legislation for possession and/or wholesale of these goods.
- Should any single active preparation of codeine not be included under Schedule 8 of the SUSDP, reports of its consumption would not be provided, under the current domestic reporting arrangements, to the OCS. This would have an effect on the accuracy of reporting of annual codeine consumption to the INCB by the Department.
- Thus, in considering the scheduling of single active liquid preparations of codeine the Committee should at the same time consider the requirements under the Convention in relation to these preparations.
- The Convention uses the term "other ingredient" in relation to preparations exempted from some provisions of the Convention. This term is taken to be consistent with the term "other therapeutically active ingredient" which is used in the SUSDP in relation to preparations of codeine.

The Committee also noted a submission from XXXXXXXX registering an interest in the outcome on this issue.

OUTCOME

The Committee agreed that further information was required to gain a better understanding of the composition of codeine linctus products in the marketplace. The Committee therefore requested that the TGA and sponsors of codeine linctus products and XXXXXXXX be approached to confirm that codeine linctus products were regarded as single active products.

In the meantime, the Committee confirmed the current scheduling of codeine and agreed that the interpretation of the current entry requires that any single active preparation of codeine, including liquid preparations, to be classified as a Schedule 8 medicine.

12.1.6 POTASSIUM CHLORIDE

PURPOSE

The Committee considered scheduling of oral potassium chloride when for therapeutic use.

BACKGROUND

Potassium chloride has been unscheduled for a number of years. Potassium chloride slow-release tablets have been supplied in Australia since 1967.

At the May 1982 NDPSC Meeting the Committee agreed that electrolyte balance control in patients at risk required proper supervision. No recommendations, however, were made by the Committee at this time.

At the February 1985 NDPSC Meeting the Committee agreed that warning on the use of potassium supplementation being given to patients on potassium sparing diuretics was the responsibility of the doctor or pharmacist and that no scheduling action was required. The February 1986 NDPSC Meeting confirmed that no entry was required in the SUSDP for potassium chloride.

At the October 2005 NDPSC Meeting the Committee discussed a XXXXXXXX Report into the death of a child from an overdose of slow release potassium chloride. XXXXXXXX recommended that slow release potassium chloride products be included in Schedule 4. Accordingly, it was agreed to gazette this substance for formal consideration at the February 2006 NDPSC Meeting. The Members also noted that potassium chloride had a wide range of uses. There was general agreement that the consideration of this issue at the February 2006 NDPSC Meeting would be confined to specifically considering the therapeutic uses of potassium chloride.

DISCUSSION

The Committee noted that potassium was scheduled in New Zealand as follows:

General Sale – POTASSIUM for external use; for internal use except when specified in the First Schedule to the Medicines Regulations 1984; for oral rehydration therapy, parenteral nutrition replacement or dialysis.

Pharmacy Only – POTASSIUM except when specified elsewhere in this Schedule; for internal use in slow release or enteric coated forms; in medicines containing more than 100 milligrams per recommended dose except in medicines for oral rehydration therapy, parenteral nutrition replacement or for dialysis.

The Committee recalled that the XXXXXXXX Report into the death of a child from an overdose of slow release potassium chloride included a number of recommendations directed to XXXXXXXX and the NDPSC. These recommendations were:

- As a matter of priority, all slow release potassium products should be given a Schedule 4 classification to ensure that they are taken under medical supervision.
- All manufacturers of slow release potassium products should be required to include on their labels the following warnings:
    - "Do not use for children"

- "Keep out of reach of children"; and
- "Seek immediate medical assistance if too many tablets are taken".

And to amend their Product Information (PI) leaflets and Consumer Medicine Information (CMI) leaflets accordingly.

- Consideration should be given to imposing a similar labelling requirement for all products that are suitable only for adult consumption and could be fatal if ingested by children.

The Members considered a submission from XXXXXXXX - proposing a rescheduling to Schedule 4, i.e. to ensure they are only taken under medical supervision, for the currently approved indication on the ARTG ("treatment and specific prevention of hypokalaemia"). The submission proposed the following wording for a potassium chloride Schedule 4 entry:

POTASSIUM CHLORIDE in oral preparations containing potassium chloride as the active pharmaceutical ingredient.

The Committee particularly noted the following points from XXXXXXXX submission:

- Slow-release potassium chloride is used primarily by elderly patients who have been prescribed certain diuretics.
- Although potassium chloride was unscheduled, XXXXXXXX tablets are often prescribed to patients and the product is listed on the Schedule of Pharmaceutical Benefits.
- The submission acknowledged that the Committee may consider Schedule 3 a more suitable category for slow-release potassium chloride.
- There was a paucity of specific toxicological and clinical data available on slow-release potassium chloride preparations. An overdose of potassium chloride would produce hyperkalaemia, which could lead to serious toxic effects, including cardiac arrest and death. Patients with impaired renal function, diabetes and cardiovascular disease as well as children could develop hyperkalaemia-related toxicity at doses lower than those recommended for adults.

An evaluation of the XXXXXXXX submission was undertaken which noted:

- Current Australian approved indications are for the treatment and specific prevention of hypokalaemia (e.g. during diuretic therapy and in GI disorders with potassium loss, such as diarrhoea, vomiting, fistula drainage, enterostomy or laxative abuse).
- XXXXXXXX had provided a Periodic Safety Update Report for XXXXXXXX from 1/8/97 to 28/2/01 and the Council for International Organizations of Medical Sciences listings for XXXXXXXX from 2001, including the initial and follow up reports of the death of the child referred to the XXXXXXXX. There were no unexpected or new adverse event profiles seen in these reports other than the childhood fatality.

- XXXXXXXX noted that existing information on overdose of potassium chloride appeared in the approved PI for XXXXXXXX, including issues of hyperkalaemic toxicity potentially leading to cardiac arrest.
- It was also noted in the PI that administration of potassium chloride slow release tablets had been associated with serious GI effects including intestinal wall perforation and that in patients with impaired renal function or cardiovascular disease, serum potassium needed frequent monitoring during treatment with XXXXXXXX.
- It was argued by XXXXXXXX, and the evaluator agreed, that the clinical uses and risks associated with potassium chloride are well understood by medical practitioners although consumers may not have a clear understanding of these risks.
- Because there are few people in the community who are potassium depleted to the point of requiring potassium supplementation, it seemed unlikely that restricting supply of potassium chloride tablets to prescription only would have a significant public health impact.

The Members also noted that the following analysis from the Evaluation Report of XXXXXXXX proposed changes in the PI and CMI for XXXXXXXX:

- Under precautions, "Children", it is stated that "XXXXXXXX should not be used in children". Also in the CMI under "Things you must not do", it is stated "Do not give XXXXXXXX to children".
- In the CMI "How much to take" it is stated that "It may be necessary to take more XXXXXXXX tablets per day but never increase the dose without your doctor's advice".
- It is proposed that statements regarding natural sources of potassium such as bananas, avocados, etc. be removed "to give patients more accurate understanding of the risks associated with potassium supplements": the evaluator considers that these statements should be retained, as excess natural sources of potassium may in certain cases impact on potential toxicity.
- XXXXXXXX had not included any statements to modify the PI/CMI to fit in with the other two recommended warning statements of "keep out of the reach of children" and "seek immediate medical assistance if too many tablets are taken"; these should be included in the revised PI and CMI. In addition, the evaluator considers that in line with the recommendations from the XXXXXXXX Report, PI/CMI statements and labelling indicating that XXXXXXXX could be fatal if ingested by children should be included.

The Members further noted that the Evaluation Report supported the proposal to reclassify XXXXXXXX tablets to Schedule 4, providing the additional warning statements, as discussed and as recommended by XXXXXXXX are included in the PI/CMI and warning labels.

The Committee was advised that XXXXXXXX was provided with a copy of the evaluation report and submitted a pre-meeting comment. The Committee particularly noted:

- With regard to XXXXXXXX proposal that statements regarding natural sources of potassium be removed:
    - XXXXXXXX acknowledged that the evaluator considers that these statements should be retained and agreed to reinstate these statements into the CMI.
    - For clarity, XXXXXXXX felt this should be followed by appropriate advice to patients taking XXXXXXXX that their dose may need to be adjusted, if their diet is rich in natural sources of potassium, but never changed without their doctor's advice. The Members noted that XXXXXXXX would like the opportunity to negotiate the exact wording of this statement directly with the TGA, after the NDPSC considers this proposal.
- With regard to concerns about various additional warning statements:
    - XXXXXXXX noted the Evaluator's concerns that "keep out of the reach of children" and "seek immediate medical assistance if too many tablets are taken" were not included in the PI/CMI. However, the PI already includes a statement in the section "Use in children" that the safety and effectiveness of XXXXXXXX had not been established in children and that the tablets should not be used in children. XXXXXXXX have, however, agreed to include these two additional statements in the PI.
    - XXXXXXXX also noted that the above statements already appeared in the CMI under the heading "If you take too much (overdose)", which XXXXXXXX felt complied with this particular prerequisite.
    - In addition, XXXXXXXX noted the Evaluator's recommended that the PI/CMI statements should indicate that XXXXXXXX could be fatal if ingested by children. XXXXXXXX presumed that this proposal was based on XXXXXXXX recommendation that consideration should be given to imposing the aforementioned labelling requirement to all products that are suitable only for adult consumption and could be fatal if ingested by children.
    - XXXXXXXX again noted the statements included in the PI, discussed above, and asserted that the additional statement proposed by the evaluator did not appear to be consistent with this existing advice. As an alternative XXXXXXXX would consider the inclusion of advice in the PI and CMI to indicate that this product is only suitable for use in adults and should not be given to children. XXXXXXXX feel this alternative would be consistent with existing information in these documents, as well as the XXXXXXXX recommendation. XXXXXXXX would like the opportunity to negotiate the exact wording of this statement directly with the TGA, after the NDPSC considers this proposal.
- Regarding changes to the container label:

- XXXXXXXX noted that the only additional change recommended by the evaluator was inclusion of a statement to indicate that XXXXXXXX could be fatal if ingested by children.
- XXXXXXXX had proposed to include a statement on the label that XXXXXXXX was only suitable for use in adults and should not be given to children, for the reasons described above and in keeping with the proposed changes to the PI and CMI.

- Finally, XXXXXXXX noted that the evaluator specifically referred to XXXXXXXX in making the various recommendations and it was unclear whether the intention was to restrict the reclassification to XXXXXXXX brand. The Members were advised that this issue had been clarified with the XXXXXXXX and that any changes to the SUSDP would apply to all presentations of potassium chloride slow-release tablets available on the Australian market.

The Members were also advised of a number of case line listings involving potassium chloride obtained from the TGA covering the period from May 1994 to the present. Although potassium chloride was present for a number of deaths Members noted the presence of other medicines suspected of contributing to these fatalities.

The Committee considered a submission from XXXXXXXX proposing that slow-release potassium chloride preparations be placed into Schedule 3 with the mandating of child-resistant packaging. Members particularly noted:

- While these preparations have been available in Australia for about 40 years unscheduled they are nearly always supplied on prescription (although some non-concession patients purchase them without prescription because of cost).
- Use of these products has declined in recent years owing to the greater use of potassium-sparing diuretics and less reliance on thiazides and loop diuretics for hypertension.
- Access to the slow-release potassium chloride by the child mentioned in the XXXXXXXX Report would not have depended on whether the medicine was obtained with or without a prescription.
- The proposed statement “do not use for children” would be applicable only if the medicine were in a schedule other than Schedule 4.

The Committee was advised that in addition to XXXXXXXX there were at least two equivalent potassium chloride slow-release products (both 600 mg formulations) available on the Australian market: XXXXXXXX and XXXXXXXX.

The Members considered a submission from XXXXXXXX also noting that potassium chloride was used in listable medicines as an excipient material. XXXXXXXX, while accepting the reasons for the possible Schedule 4 inclusion of potassium chloride, requested that the wording of the entry should exclude potassium chloride when used as an excipient.

The Committee also considered a submission from XXXXXXXX which recommended that the Committee's consideration focus on slow release potassium chloride only. XXXXXXXX also advised that it had located 80 listed products that use potassium chloride as an excipient.

The Committee noted that according to the ARTG a number of multivitamin supplements contained potassium chloride in concentrations up to 60 mg per tablet. Members were also advised that in the UK food supplements can contain up to 200 mg potassium chloride per tablet and that the exemption to general sale for products (apart from various specified therapeutic uses) in New Zealand was 100 mg.

The Members considered a submission from XXXXXXXX supporting, rather than an S4 classification, harmonisation of potassium chloride scheduling in line with the pharmacist only restrictions in New Zealand. XXXXXXXX:

- Noted that this would be consistent with the observations at the October 2005 NDPSC Meeting that despite the unscheduled status distribution has always been restricted to Pharmacy. XXXXXXXX asserted that this would provide a suitable opportunity for healthcare professional intervention as to ensuring the appropriateness of the purpose by a consumer.
- Noted the use of potassium chloride in oral rehydration therapy products and asserted that these products do not warrant any scheduled status. XXXXXXXX recommended, therefore, that any schedule entry specify that the potassium chloride be for a therapeutic purpose so as not to encompass the complexed excipient forms.

Members considered the merits of a lower scheduling for high dose oral potassium chloride products than the recommended Schedule 4. The Committee noted that the current unscheduled status of slow release potassium chloride products technically allowed them to be available through retail outlets. However, a Member asserted that these products had been marketed for a long time and had always been supplied through pharmacies (i.e. treated as though they were Schedule 2 products). Indeed, a Member observed that many pharmacies keep these products in the dispensary. A Member further noted that Schedule 2 would be in line with the current New Zealand entry for slow release preparations. The XXXXXXXX Member confirmed this but acknowledged that this classification was probably not consistent with the safety profile of high dose potassium chloride and that it should be Schedule 4. Additionally, a Member noted that if the slow release potassium chloride product involved in the death of the child had been Schedule 2 the child would still have been at the same risk as the product was bought from a pharmacy anyway. The Committee therefore agreed to a Schedule 4 entry for potassium chloride.

The Committee considered limiting the Schedule 4 entry to slow release potassium chloride. However, the Members instead agreed to a broader "oral preparations for therapeutic use" as it was noted that otherwise there are high dose potassium chloride mixtures that were just as toxic as the slow release formulations which would escape the Schedule 4 entry. The Committee also agreed that a general exemption for products

containing less than 100 mg potassium chloride was appropriate as there was little risk from this concentration. A 100 mg exemption would also allow the continued low level use as an excipient or in multi-vitamin type products. Members further noted that a 100 mg exemption would be in line with the similar New Zealand.

Members also noted concerns in some submissions regarding oral rehydration therapy and agreed that an exemption for this use was appropriate. Following discussion by the Committee to identify any other inadvertent impacts of the proposed Schedule 4 entry, an exemption for enteral feeding was also agreed to. The Committee further agreed that, given the particular risk to children from high dose potassium chloride products, to recommend to the XXXXXXXX that child-resistant closures be mandatory for these products.

DECISION 2006/46 - 27

The Committee agreed

- To include oral potassium chloride (>100 mg per dosage unit) for therapeutic use in Schedule 4 on the grounds that its toxicity profile required professional oversight.
- To exemptions for oral potassium chloride preparations containing than > 100 mg per dosage unit for oral rehydration therapy and for enteral feeding.
- To recommend to the Drug Safety and Evaluation Branch of TGA that, to minimise any potential harm to children, child-resistant closures be mandatory for the scheduled potassium chloride products.

Schedule 4 – New entry

POTASSIUM CHLORIDE in oral preparations for human therapeutic use **except**:

(a) when containing 100 mg or less of potassium chloride per dosage unit;

(b) in preparations for oral rehydration therapy; or

(c) in preparations for enteral feeding.

12.1.7 LEVONORGESTREL

PURPOSE

The Committee considered a proposal to amend the Schedule 3 entry for levonorgestrel to accommodate a single 1.5mg tablet.

BACKGROUND

Levonorgestrel, the active isomer of norgestrel, is a progestogen. Oestrogen and progestogen combinations have been used for post-coital contraception with the proviso that they are taken soon after unprotected sexual intercourse and use should be restricted to emergency situations rather than as a routine method. The precise mechanism for levonorgestrel's activity as a post-coital emergency contraceptive is uncertain; it is thought to work mainly by preventing ovulation and fertilisation, by altering tubal transport of sperm and/or ova and/or by affecting implantation.

At the November 1988 meeting levonorgestrel was included as an individual entry in Schedule 4 of the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP). Prior to that date, levonorgestrel was included in a generic Schedule 4 entry for sex hormones.

XXXXXXXX was included in the Australian Register of Therapeutic Goods (ARTG) on 9 October 2001 with the approved indication as *"An oral emergency contraceptive indicated for use within 72 hours of unprotected intercourse. It should only be used as an emergency measure. Women who present for repeated courses of emergency contraception should be advised to consider long-term methods of contraception."*

The additional tradename of XXXXXXXX for XXXXXXXX was registered in the ARTG on September 2002. When registered, the recommended dose for emergency contraception was 2 tablets of 0.75mg levonorgestrel each, 12 hours apart, within 72 hours after unprotected intercourse.

At the October 2003 Meeting, the Committee confirmed it's June 2003 decision to include levonorgestrel, in a two tablet pack of 0.75mg per tablet, for emergency post-coital contraception in Schedule 3 of the SUSDP. The decision was based on established safety and efficacy of the product, the need for timely access and the fact that it had been available OTC in several countries for a number of years. It was also based on the requirement for pharmacists to give professional advice and counselling to consumers on the safe and effective use of this product. This decision came into effect through State and Territory legislation on 1 January 2004.

DISCUSSION

The Committee considered an application from XXXXXXXX seeking for a variation in the wording of the Schedule 3 entry for levonorgestrel. The request related to a proposed change of dosage regime, i.e. a single dose of 1.5mg levonorgestrel (one 1.5mg tablet or two 0.75 mg tablets) instead of two doses of 0.75mg levonorgestrel taken 12 hours apart but within 72 hours after unprotected intercourse. Members noted the documents provided by the applicant. These included an extract of MEC Minutes from June 2005 Meeting, a Clinical Evaluation Report (CER) and an overview by TGA, a Periodic Safety Update Report (PSUR) for levonorgestrel from 1 January 2004 – 30 June 2004, amended Product Information and Consumer Medicine Information.

Members noted from the minutes of the June 2005 MEC Meeting that the MEC recommended approval of the revised dosage regime for XXXXXXXX, so that two 0.75mg tablets can be taken together as a single dose, as soon as possible after unprotected intercourse, with treatment to be given not later than 72 hours after unprotected intercourse. Members also noted the MEC's evaluation of the sponsor's submission which included data from the original registration application, recent references and a clinical expert report. The data assessed was as follows:

i. Pharmacokinetics. A published study (Johansson et al, 2002) of five healthy women aged 18-45 years showed that overall equivalent levonorgestrel serum levels were obtained with the single dose of 1.5mg levonorgestrel or two doses of 0.75mg taken 12 hours apart.

ii. Efficacy. The pivotal study was a double-blind, randomised, double dummy multicentre trial conducted in ten countries by the WHO/ HRP (Von Hertzen et al, 2002). Of the 4,071 women enrolled for whom follow-up data was available, 1,356 women took either levonorgestrel regimen (2 x 0.75mg levonorgestrel at once or two doses of 0.75mg levonorgestrel administered 12 hours apart). There was no significant difference in efficacy between the two levonorgestrel treatment groups: twenty women (1.5%) in the single dose group became pregnant with 81.9% of expected pregnancies prevented (CI: 72.1 – 88.9) while 24 women in the two dose group became pregnant (1.8%) with 77.3% of expected pregnancies prevented (CI: 66.3 – 85.5). A second efficacy study (Arowojolu et al, 2002) compared efficacy of single dose *vs* two dose treatment (n = 1,118) and concluded that both treatment regimens were effective, with the single 1.5mg dose appearing slightly more effective. It was noted that this second study used a formulation different to the one marketed in Australia.

iii. Safety. There was no significant difference in adverse events for either treatment regime in the pivotal study. Headache & breast tenderness were reported significantly more frequent ($p<0.05$) with the single dose in the supporting study but all side effects were reported as mild & short term. One ectopic pregnancy was reported in the two dose regimen in the pivotal study.

Members noted that the clinical evaluator had concluded that the submitted studies provide evidence that a single dose of 1.5mg of levonorgestrel is as effective, and may be slightly more effective, compared with the currently recommended dose of two 0.75mg levonorgestrel tablets taken twelve hours apart.

It was also noted by members that the six monthly PSUR revealed a total of 49 adverse events reported in 41 subjects, including 33 cases of unintended pregnancy (6 of them were ectopic pregnancies and 3 were spontaneous abortions). The rate of ectopic pregnancies was found to be comparable with the previous 12 months. In summary, over the period covered by this report, no significant change was found in the characteristics of adverse events experiences in patients receiving levonorgestrel for emergency contraception. **[**Section deleted**]**

[Sentence deleted**]**. Members also noted pre-meeting submissions from XXXXXXXX and XXXXXXXX supporting the proposed amendment.

Members appreciated that the availability of levonorgestrel under Schedule 3 has allowed timely access to this drug by consumers, and furthermore, the recent clinical evidence showed comparable bioavailability, efficacy and potential side effects between the two doses of 0.75mg taken 12 hours apart and the proposed single dose of 1.5mg levonorgestrel. While there was an agreement to amend the Schedule 3 entry for levonorgestrel to accommodate the use of either a two tablet pack of 0.75mg per tablet, or a one tablet pack of 1.5mg tablet as a single dose, the Committee accepted some members' view that the substance for a particular indication, rather than a dose regime, should be included in the schedule entry. Any limitation for the dose regime would be assessed as part of the registration process for a product. Hence, the Committee agreed to amend the Schedule 3 entry for levonorgestrel for emergency post-coital contraception without specifying a particular dose regime.

DECISION 2006/46 - 28

The Committee agreed to amend the Schedule 3 entry for levonorgestrel for emergency post-coital contraception without specifying a particular dose regime. This amendment shall accommodate the proposed use of a single 1.5mg tablet pack as well as a two tablet pack of 0.75mg per tablet, on the basis of their comparable bioavailability, efficacy and potential side effects.

Schedule 3 - Amendment

LEVONORGESTREL - Amend entry to read:

LEVONORGESTREL for emergency post-coital contraception.

12.2 SUSDP, PART 5

12.2.1 ORLISTAT

PURPOSE

The Committee considered a new application submitted by XXXXXXXX seeking the inclusion of orlistat in Appendix H.

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 XXXXXXXX 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. XXXXXXXX was marketed in Australia by XXXXXXXX in May 2000 as a prescription medicine.

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 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; the necessity for medical assessment to determine a patient's suitability for treatment with orlistat; and 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. In making this decision, the NDPSC also took into account that several weight management programs/protocols had been developed by the sponsor and the pharmacy profession which were designed to assist consumers in achieving safe and long term weight loss with orlistat therapy. The Schedule 3 amendment for orlistat came into effect on 1 May 2004.

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 could potentially 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.

DISCUSSION

During consideration of post meeting comments at the October 2005 NDPSC Meeting, the Committee noted that a new submission seeking inclusion of orlistat in Appendix H had been received from XXXXXXXX. This application reiterated its arguments on the public health benefit of advertising orlistat, with the following points highlighted at the February 2006 meeting:

- Market research suggests the public already view diet and exercise as the first option for weight loss, and 'a pill' as the last resort.
- Although pharmacotherapies are considered by the NHMRC as a fourth line treatment for the management of overweight/obesity after diet, exercise and counselling/behavioural therapy, many people fail to lose weight using diet and exercise alone.
- Obesity experts support the need for adjunctive therapy for weight-loss such as XXXXXXXX on the basis that for many people diet and exercise alone are not sufficient.
- There are more risks (diabetes mellitus, insulin resistance, hypertension, hyperlipidaemia, ischaemic heart disease) associated with obesity than with orlistat therapy. The use of orlistat as an adjunct to diet and exercise will improve many of these conditions. Even a modest reduction in body weight will lead to a reduction in risk.
- Pharmacists are confident to discuss and make recommendations to consumers about weight-loss methods and XXXXXXXX. The branded advertising of XXXXXXXX will direct consumers to their pharmacist for advice as to whether XXXXXXXX is suitable for their condition.
- The Therapeutic Goods Advertising Code (TGAC) requires promotion of weight-loss products to be carried out giving due balance to therapeutic claims and diet and exercise. The CMI and packaging recommend XXXXXXXX use in conjunction with diet and exercise, not as a first-line therapy. A branded advertising campaign cannot promote XXXXXXXX as first-line therapy.
- XXXXXXXX works more effectively as an adjunct to diet and exercise. The XXXXXXXX Patient Support Programme has been specifically designed around diet and exercise.

The evaluator, noting the extensive arguments and relevant information/evidence provided by the sponsor, supported the inclusion of orlistat in Appendix H. Members were informed by the evaluator that additional references provided in the present application support the effectiveness of orlistat, and readiness of consumers and pharmacists for advertising of orlistat. The following points were highlighted:

- In a recent post-marketing surveillance (uncontrolled) study carried out in Germany over 15000 patients took part in a nine month trial (Wirth. Diabetes,

Obesity and Metabolism 2005, 7:21-27), orlistat use led to reduction of cholesterol by 11%, of blood pressure by 8.7/5.1 mm Hg and of blood glucose by 7.5%. Patients who were under treatment for hypertension, dyslipidaemia or diabetes showed a further decrease of the parameters as well as reduced dose of medications.

- A survey in The Sydney Morning Herald (27 March 2003, n = 2587) indicated that 72% of participants considered eating less and exercising more as the most effective weight loss plan. In consumer research carried out in March 2003 by The Leading Edge, (XXXXXXXX), in response to the question "what do people consider as their first option for weight loss?", 92% of participants (n=706) responded that diet and exercise was the only effective measure. To another question "what is the last option for weight loss?", 76% considered taking a pill to help weight loss was the last resort.
- In a commissioned market research study (June 2005) to assess urban and rural pharmacists' (n=100) opinions of branded advertising of orlistat, 100% pharmacists were confident and 85% very confident to discuss and make recommendations about orlistat with customers; and 97% were confident to discuss and make recommendations regarding weight loss methods.
- At the February 2005 NDPSC Meeting, the evaluator had supported the proposal to include orlistat in Appendix H with the condition that reference to the modest efficacy and reduction of efficacy long-term seen in the clinical trial setting and potential side effects of orlistat need to be presented in any advertising for XXXXXXXX under the rubric of balanced, informed and non-misleading advertising. The evaluator had also suggested statements such as the following to be made in any advertising for XXXXXXXX:

  "*Orlistat may only lead to minor weight loss in some people*"
  "*Some people may experience side effects with orlistat particularly if diet is not adhered to*"
  "*People may require vitamin replacement during orlistat therapy.*"

- The Therapeutic Goods Advertising Code (TGAC) had been strengthened in August 2005 and that there are more stringent requirements regarding the advertising of weight loss products.
- Providing that appropriate caveats for efficacy and safety are included in advertising, the evaluator considered that it would be reasonable, on public health grounds, to allow inclusion of this S3 product in Appendix H of the SUSDP.

The Committee noted that pre-meeting comments were received from XXXXXXXX, XXXXXXXX, and XXXXXXXX, supporting an Appendix H listing for orlistat. All respondents contended that oristat is a thoroughly researched and well understood weight-loss product, and the advertising will only send a balanced message overall and direct consumers to seek a pharmacist's counsel and further information provided by the

sponsor. It was argued that potential public health benefit shall be gained by indirectly managing other obesity related risk factors. Additionally, it was contended that the current advertising restrictions on orlistat have potential disadvantages in that consumers may not be aware of this product and not fully realise the health benefits of orlistat therapy.

The Committee appreciated that obesity is a major public health concern in Australia. It was understood that 67 percent of adult males and 52 percent of adult females were overweight or obese in 1999-2000 (NHMRC Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults – 2003).

Members extensively discussed the potential risk and benefit of Appendix H listing of orlistat based on the information provided by the sponsor and pre-meeting respondents, and in light of the changes to the TGAC.

The Committee considered that if direct to consumer advertising of XXXXXXXX was to be supported, the modest efficacy and side effects of the product needed to be presented in a balanced way from a public health perspective. The Committee noted that the advertising of XXXXXXXX would be regulated through the Therapeutic Goods Advertising Code Council (TGACC). In August 2005 the TGACC advised the NDPSC of amendments to section 7(3) of the TGAC to ensure that messages about the importance of diet and exercise in achieving weight loss at least match the impact of any messages about benefits that the advertiser claims for the product. The TGACC believed that the provisions of the TGAC, in conjunction with the role of the mandatory pre-approval process and the active use of the Complaints Resolution Panel, are sufficiently robust in terms of effectively regulating the advertising of any weight loss products.

The Committee found reassuring that any branded advertising of XXXXXXXX would not lead to unrealistic public expectations as it would be regulated through the TGACC. The Committee also recognised that orlistat for weight loss purposes (XXXXXXXX) has been available as a Pharmacist Only (S3) Medicine since 1 May 2004, i.e. the pharmacy profession has had almost two years experience with the supply of XXXXXXXX as a Schedule 3 medicine without branded advertising. The Committee was aware that pharmacist's counselling of consumers on the use of XXXXXXXX for weight-loss had been supported by the PSA protocol 'Provision of orlistat as a Pharmacist Only medicine', professional education and training programs as well as consumer support materials. Additionally, the Consumer Product Information for XXXXXXXX recommends its use in conjunction with a low fat, calorie controlled diet and exercise.

DECISION 2006/46 –29

The Committee agreed to include orlistat in Appendix H on the grounds of potential public health benefit. The Committee noted additional information on post-marketing surveillance study, media survey and consumer/market research, as well as the experience gained by pharmacists on screening and consulting patients on the suitability of orlistat for other condition. The Committee also believed that the newly amended TGAC which

has been strengthened with regards to the advertising of weight loss products shall ensure responsible and appropriate banded advertising of the orlistat product (XXXXXXXX) by the sponsor.

Appendix H – New entry

Orlistat.

12.2.2

[Item deleted**]**

12.2.3 CETIRIZINE

PURPOSE

The Committee considered post-meeting comment in relation to the October 2005 decision to remove cetirizine for oral use from Appendix K and Appendix F Part 3 of the SUSDP.

BACKGROUND

Cetirizine hydrochloride, a piperazine derivative and metabolite of hydroxyzine, is described as a non-sedating antihistamine which is long-acting and has some mast-cell stabilising activity. It is used for the symptomatic relief of allergic conditions including rhinitis and chronic urticaria.

The October 2005 NDPSC meeting considered an application from XXXXXXXX to remove the Appendix K and Appendix F, Part 3 requirements for a sedation warning for oral cetirizine medicines administered in daily doses of up to 10 mg. The Committee noted that the evaluator of XXXXXXXX application recommended that cetirizine (and loratadine) are non-sedating in the majority of studies conducted, however, the evaluator also recommended that the Committee consider the "possibility" of sedation in some patients. Based on available evidence, the Committee agreed that cetirizine has equivalent sedation potential to loratadine and agreed to remove cetirizine from Appendix K of the SUSDP. Accordingly, the Committee also amended the wording of Appendix F, Part 3 for antihistamines to similarly remove the requirement for sedation warnings on the label of S2 cetirizine products. Taking into account the concerns raised at the meeting in regards to the potential for all sedating antihistamines to cause sedation in some patients, the Committee further agreed to refer the issue in relation to the need to include a sedation warning for all antihistamines to the Medicine Evaluation Committee (MEC) to check for consistency with the New Zealand label requirements.

DISCUSSION

The Committee noted that post-meeting comment was received from XXXXXXXX seeking to amend the Record of Reasons in relation to the October 2005 decision to remove the requirement for sedation warnings on the label of cetirizine oral preparations. XXXXXXXX disagreed with the Committee's decision to remove cetirizine from Appendix K and Appendix F, Part 3 of the SUSDP and requested that the Committee reconsider its decision. The Committee noted the following points raised in XXXXXXXX submission:

- NDPSC had no basis for the removal of the sedation warning for cetirizine since the assertion that cetirizine is no more sedating than loratadine is incorrect. It is misleading and incorrect to assert that cetirizine XXXXXXXX is no more sedating than loratadine XXXXXXXX when there is a recognised difference. The TGA makes a clear distinction between loratadine and cetirizine in the approved PI and the Record of Reasons incorrectly quoted the cetirizine PI. The correct reference in the XXXXXXXX PI presents a different picture of the CNS potential for cetirizine than that which appeared in the Record of Reasons. It is clear that doses of 20 mg cetirizine are associated with CNS effects while the XXXXXXXX PI states that tests have not shown any significant difference between XXXXXXXX 10 mg and placebo with respect to interaction with the CNS or impairment performance.
- The TGA-approved XXXXXXXX PI is consistent with the 2004 Medsafe review Classification of Sedating Antihistamines which noted CNS effects above a dose of 10 mg cetirizine. These are two independent assessments of the same data set and the objective CNS performance studies included in the Medsafe review were published in the period 1987 to 1998. There had been no new published objective data in seven years.
- From the October 2005 Record of Reasons, the NDPSC incorrectly infers that loratadine is sedating. Loratadine is classified as non-sedating by the TGA whereas cetirizine is not. It is expected that the TGA would have conducted a fair and unbiased assessment of both published and unpublished data and is in a position to compare these two drugs.
- The NDPSC basis for the decision is not consistent with the results from a large cohort study of 43,363 patients that compared sedation with cetirizine and loratadine. Mann et al (2000) conducted a large post marketing surveillance study in 43,363 patients in the UK designed to measure differences in adverse events between loratadine, cetirizine, fexofenadine and acrivastine. The study found that cetirizine was 3.5 times more likely to result in reports of sedation than loratadine. The author's advice that where sedation is undesirable, loratadine is preferred over cetirizine is a recommendation that recognises there is a difference in this side effect between the two drugs that has practical relevance.
- The approved dosage range for cetirizine is 10-20 mg. The literature indicates that at high dose, cetirizine is associated with CNS effects and adverse event rates increase

with increased dose, being significantly greater than placebo even at the low dose. It is not possible on this basis to conclude that cetirizine is no more sedating than loratadine as loratadine at its approved dose is not associated with CNS effects or with an increased rate of sedating side effects above that seen with placebo.

- The NDPSC was incorrect in comparing the effects seen with unapproved doses of loratadine to effects seen at approved doses of cetirizine and thereby concluding that the two had the same rates of sedation. The rates of sedation are different when approved dosages are compared.
- Under the *Therapeutic Goods Act*, it is an offence to promote dosages other than approved dosages. This is critical to the assessment of the relative sedation rates for cetirizine and loratadine since these are the doses that will be used by the general population. This was not taken into proper account and the NDPSC had formed an incorrect conclusion about the relative rates of sedation between cetirizine and loratadine that does not protect public safety.

The Committee noted the advice received from XXXXXXXX which raised the following points:

- **[**Section deleted**]**
- XXXXXXXX application to the NDPSC proposing changes to the SUSDP included considerably more data than that submitted to the TGA's Over-The-Counter Medicines Section (OTC) in support of the requested changes to the PI. The data submitted to OTC did not support a dilution of warnings relating to drowsiness either in the PI or on the labels for products containing cetirizine.
- the December 2005 MEC meeting recommended that:
  - NDPSC be advised that MEC was unwilling to recommend removal from RASML of the requirement to include a 'drowsiness' warning on the labels of products containing cetirizine on the basis of the data provided to date.
  - Before this matter can proceed, the sponsor should provide a comprehensive review of the literature (as specified in the ARGOM) regarding the sedative / CNS depressant effects of cetirizine, together with copies of all relevant references identified by a proper literature search.

Members noted the paper by Mann (BMJ Volume 320, 2000) included in XXXXXXXX post-meeting submission was a post-hoc analysis of data from prescription-event monitoring studies which aimed to show the relative sedation rates between loratadine, acrivastine, fexofenadine and cetirizine. The Committee noted the post-meeting comment based on this article that cetirizine was associated with 3.5 times more reports of sedation than loratadine. However, it was also noted that the doses associated with cetirizine's sedative/CNS effects were not defined in the Mann paper.

The Committee noted that Australia and New Zealand had several oral products containing cetirizine (liquid and solid dose forms) on the ARTG and SMARTI database.

As stated in the sponsor's application, the TGA's approved maximum daily dose for XXXXXXXX 10 mg is 20 mg per day in adults, 10 mg for children aged 6 years and over, and 4-10 mg for children aged 1-6 years depending on body weight. Members noted that the sponsor had submitted data to support its claim that the recommended daily dose of 10 mg cetirizine taken orally is no more sedating than the recommended dose of loratadine 10 mg taken orally. The sponsor further gave an undertaking that it would amend the current labels for XXXXXXXX products to reflect a recommended maximum daily dose of 10 mg cetirizine, if its application before the NDPSC was successful.

The Committee recalled that the evaluation report considered at the October 2005 NDPSC meeting supported the view that 10 mg cetirizine did not result in any impairment compared to placebo in actual driving tests, psychomotor and cognitive tests (Theunissen et al. 2004) and was comparable to 10 mg loratadine in terms of sedation potential. Whilst the evaluation report supported the removal of cetirizine from Appendix K and Appendix F, Part 3 of the SUSDP, the evaluator also recommended that consideration of the statements referring to the 'possibility' of sedation in some patients should be considered for consistency with the UK and NZ labelling approach for second generation antihistamines.

The Committee reviewed the arguments put forward by members at the October 2005 meeting and the following issues were noted:

- Appendix F sets down warning requirements for OTC preparations while Appendix K sets down sedation warning requirements for dispensed medications at any dose.
- A member pointed out that XXXXXXXX most of the data presented in support of XXXXXXXX application focused on the sedation potential of a dose of 10mg of cetirizine in clinical trials. The Member reminded the Committee that the SUSDP Schedule 2 entry for cetirizine did not have a dosage cut-off but specified cetirizine "in preparations for oral use". Thus, regardless of what dosage XXXXXXXX intends, other sponsors could potentially market a 20mg tablet, or a doctor could prescribe a dose of cetirizine higher than 10mg, and neither would require a sedation warning should this scheduling amendment take place.
- XXXXXXXX pointed out that Canada was the only country listed in the sponsor's submission which did not require a sedation warning on the package but still required warning statements within the PI and CMI documents.
- New Zealand required sedation warnings for both loratadine and cetirizine, i.e. "Although this medicine is unlikely to affect your ability to drive or operate machinery, a few people may be impaired and care should be taken". A member suggested that since XXXXXXXX indicated that presentations containing up to 10mg of cetirizine and presentations containing 10mg of loratadine should be subject to the same labelling requirements, it might be more appropriate for Australia to take the same stance as New Zealand and require sedation warnings for both rather than for neither. At the very least, the Member suggested that the S2 entry for cetirizine should be limited to 10mg.

- Comment was made that while the Appendix F warning statements 39 and 40 both warn of the potential for interaction with alcohol, this issue was not addressed in XXXXXXXX submission.

Furthermore, the Committee noted that MEC did not support the removal of sedation warnings from cetirizine products having considered XXXXXXXX application to change the required statements in the PI document regarding the sedation potential of cetirizine. Members agreed that the approved recommended daily dosage levels based on approved indications for cetirizine products were crucial issues to be taken into account when considering the label requirements for products and that this matter would be appropriately dealt with at registration.

With regard to the sponsor's proposal to remove the requirement to label oral preparations containing 10 mg or less of cetirizine, members noted that the available data supported the conclusion that cetirizine's sedation potential increased with the dose and that removing the sedation warning on oral preparations containing 10 mg or less of cetirizine would not take into account the full recommended daily dosage range of all cetirizine products in S2.

DECISION 2006/46 – 30 (Set Aside Decision 2005/45 – 19)

Whilst the Committee accepted that the data submitted by the applicant and the evaluation report may support the contention that 10 mg cetirizine was comparable to 10 mg loratadine, the approved maximum recommended daily dosage for existing cetirizine products in S2 was up to 20 mg day. The Committee recognised that the proposal by the applicant to limit the maximum recommended daily dosage for its S2 cetirizine products to 10 mg, if the application was successful, could have implications on the efficacy of such products if they continued to be marketed under the current approved indications. Furthermore, members noted that the new information provided to the February 2006 meeting (Mann paper) showed that cetirizine was associated with a higher number of incidences of sedation compared to loratadine and that this information needed to be reconsidered in the context of MEC's advice at the next meeting (June 2006).

The Committee also noted that as of 1 May 2006, the transfer of all mandatory label advisory statements for medicines from the SUSDP to the *Required Advisory Statements for Medicine Labels* (RASML) would take effect. After this date, the OTC Medicines Section would have full responsibility for updating and maintaining the RASML and Appendix F of the SUSDP would then cease to be the reference document for medicine label requirements.

On these grounds, the Committee agreed that it would be appropriate for XXXXXXXX application to remove cetirizine from Appendix F, Part 3 of the SUSDP to be assessed by MEC to take into account potential efficacy issues affected by the proposal to reduce the maximum daily dosage recommendations for S2 oral preparations containing cetirizine from 20 mg to 10 mg. Accordingly, the Committee agreed to set-aside DECISION 2005/45-19 which was made at the October 2005 meeting and retain the inclusion of

cetirizine in SUSDP Appendix K and Appendix F, Part 3. Furthermore, the Committee also agreed to review the inclusion of cetirizine in Appendix K of the SUSDP at the June 2006 meeting provided advice is received from the MEC with regard to the need to label dispensed cetirizine products with a sedation warning.

13. MATTERS REFERRED BY THE AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC)

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY NDPSC)

13.1.1 PALIFERMIN

PURPOSE

The Committee considered the scheduling of the new medicine palifermin.

BACKGROUND

Palifermin is a human recombinant keratinocyte growth factor (KGF) that binds to the KGF receptor, and is reported to produce proliferation, differentiation, and migration of epithelial cells.

The 241 ADEC Meeting (August 2005) recommended the approval of a submission by XXXXXXXX to register XXXXXXXX containing palifermin 6.25 mg per vial, for the indication "to decrease oral mucositis in patients with haematological malignancies receiving myelotoxic therapy requiring haematopoietic stem cell support." **[**Section deleted**]**.

DISCUSSION

[Paragraphs deleted**]**

The Committee also noted the following points from the Micromedex monograph on palifermin:

- Adverse reactions include rash, erythema, oedema, pruritus, perioral dysaesthesia, tongue discoloration and thickening, and altered taste. Fever, and gastrointestinal and respiratory disturbances have also been reported.

- The safety and efficacy of palifermin in the treatment of non-haematological neoplasms has not been established;

- Stimulation and growth of tumours have been demonstrated in animal and in-vitro studies of non-haematopoietic human tumours. However, no mutagenic or clastogenic effects were observed.

The Committee noted that palifermin is not a classified medicine in New Zealand. Due to the concern with its carcinogenic potential, members discussed the necessity for palifermin to be included in Appendix D for further control. Members noted that since the proposed indication is "to decrease oral mucositis in patients with haematological malignancies receiving myelotoxic therapy requiring haematopoietic stem cell support", palifermin will be prescribed by specialised medical practitioners only. Hence, further controls through inclusion in Appendix D were considered to be unnecessary. On the other hand, members understood that palifermin is unlikely to be used by general practitioner for treatment of patients with oral mucositis, since it is an injectable agent, and thus the cost is likely to be high.

DECISION 2006/46 - 31

The Committee agreed that palifermin be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and that its safe use required patient management and monitoring by a medical professional. The inclusion of palifermin in Appendix D is considered unnecessary since the indication and nature of the product required it to be used by specialised medical practitioners.

Schedule 4 – New entry

PALIFERMIN.

13.1.2 RASAGILINE

PURPOSE

The Committee considered the scheduling of the new medicine rasagiline.

BACKGROUND

Rasagiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain.

The August 2005 ADEC Meeting recommended approval of a submission by XXXXXXXX to register XXXXXXXX containing rasagiline 1mg for "the symptomatic treatment of idiopathic Parkinson's disease as monotherapy (without concomitant levodopa/decarboxylase inhibitor therapy) or as adjunct therapy (with concomitant levodopa/decarboxylase inhibitor therapy)". **[**Section deleted**]**

DISCUSSION

The Committee noted that rasagiline is not a classified medicine in New Zealand.

[Paragraph deleted**]**

Members also noted information in the Micromedex monograph regarding common adverse effects reported with rasagiline monotherapy, including headache, flu-like syndrome, malaise, neck pain, angina pectoris, dyspepsia, anorexia, leucopenia, arthralgia, arthritis, depression, vertigo, rhinitis, conjunctivitis, skin rashes, melanoma, and urinary urgency. Cerebrovascular accidents and myocardial infarction have been reported rarely.

DECISION 2006/46 - 32

The Committee agreed to include rasagiline in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and that its safe use required patient management and monitoring by a medical professional.

Schedule 4 – New entry

RASAGILINE.

13.1.3 OLMESARTAN MEDOXOMIL

PURPOSE

The Committee considered the scheduling of the new medicine olmesartan medoxomil.

BACKGROUND

Olmesartan is an angiotensin II receptor antagonist with actions similar to those of losartan.

The August 2005 ADEC Meeting recommended approval of a submission by XXXXXXXX to register XXXXXXXX containing olmesartan medoxomil 10 mg, 20 mg and 40 mg for "the treatment of hypertension". Olmesartan medoxomil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form olmesartan. **[**Sentence deleted**]**

DISCUSSION

[Paragraph deleted**]**

The members also noted the following points from the Micromedex monograph on olmesartan:

- Safety and efficacy has not been established in paediatric patients.
- Olmesartan is FDA approved for the treatment of hypertension.
- Due to teratogenic effects reported with angiotensin receptor antagonists, use of olmesartan during pregnancy is strongly discouraged.

The Committee noted that olmesartan is not a classified medicine in New Zealand, and no public submissions were received in response to the gazette notice.

DECISION 2006/46 - 33

The Committee agreed to include olmesartan 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.

Schedule 4 – New entry

OLMESARTAN.

13.1.4 LANTHANUM CARBONATE

PURPOSE

The Committee considered the scheduling of the new medicine lanthanum.

BACKGROUND

Lanthanum carbonate is a phosphate binder used for hyperphosphataemia in patients with chronic renal failure.

The August 2005 ADEC Meeting recommended approval of a submission by XXXXXXXX to register the new medicine lanthanum carbonate XXXXXXXX in strengths of 250 mg, 500 mg, 750 mg and 1000 mg chewable tablets for the treatment of "hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)".

[Paragraph deleted**]**

DISCUSSION

[Paragraph deleted**]**

The Committee also noted the following from the Micromedex monograph on lanthanum:

- Safety and effectiveness has not been established in paediatric patients.
- Lanthanum carbonate exhibits little systemic absorption. Following administration with food, lanthanum carbonate forms a compound of low aqueous solubility (i.e., lanthanum phosphate) which does not readily pass through the lining of the gastrointestinal tract into the blood.

- The use of lanthanum carbonate in pregnant women is not recommended. Studies in this patient population have not been conducted, including the effect of lanthanum carbonate on the absorption of vitamins and other nutrients.
- Lanthanum carbonate is an effective oral phosphate binder for the treatment of hyperphosphatemia in patients with end-stage renal disease. It appears to be a rational alternative to calcium- or aluminum-containing phosphate binders.

[Paragraph deleted**]**

The Committee noted that lanthanum is not a classified medicine in New Zealand, and no public submissions were received in response to the gazette notice.

DECISION 2006/46 - 34

The Committee agreed to include lanthanum carbonate 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.

Schedule 4 – New entry

LANTHANUM.

13.1.5 PEGVISOMANT

PURPOSE

The Committee considered the scheduling of the new medicine pegvisomant.

BACKGROUND

Pegvisomant is a growth hormone-receptor antagonist used for the treatment of acromegaly.

The October 2005 ADEC Meeting recommended the approval of a submission by XXXXXXXX to register pegvisomant XXXXXXXX 10mg, 15mg and 20mg powder for injection with diluent, for the indication “the treatment of acromegaly in patients who have had inadequate response to surgery and/or radiation and/or other medical therapies or for whom these therapies are not appropriate. The treatment goal is to normalise IGF-1 levels.”

[Paragraph deleted**]**

DISCUSSION

[Paragraph deleted**]**

The Committee also noted the following from the Micromedex monograph on pegvisomant:

- Pegvisomant represents a new way of treating acromegaly, and daily therapy has shown high efficacy in initial studies. However, concerns regarding use of pegvisomant have emerged, including the potential for hepatotoxicity, the rises in growth hormone levels observed during therapy, and the potential for anti-pegvisomant antibody formation.
- Adverse effects commonly reported with the use of pegvisomant include gastrointestinal disturbances, elevated liver function tests, flu-like symptoms, fatigue, injection site reactions, arthralgia, myalgia, headache, dizziness, somnolence, tremor, sweating, pruritus, rash, sleep disorders, hypercholesterolaemia, weight gain, hyperglycaemia, hunger, and hypertension.
- Some preclinical and clinical data suggest a potential role for pegvisomant in diabetes mellitus. The drug was shown to limit renal effects and reduce hyperglycemia in diabetic mice and improve insulin resistance in acromegalic patients.

Members noted that pegvisomant is proposed as a second line treatment for acromegaly which affects a small patient group.

The Committee noted that pegvisomant is not a classified medicine in New Zealand, and no public submissions were received in response to the gazette notice.

DECISION 2006/46 - 35

The Committee agreed to include pegvisomant 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.

Schedule 4 – New entry

PEGVISOMANT.

14. OTHER MATTERS FOR CONSIDERATION

14.1

[Item deleted**]**

14.2 BENZYLPIPERAZINE AND TRIFLUOROMETHYLPHENYLPIPERAZINE

PURPOSE

The Committee considered the scheduling of benzylpiperazine (BZP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP).

BACKGROUND

BZP is an N-monosubstituted piperazine derivative. BZP, available as either the base or as a hydrochloride salt, was first synthesized in 1944 as a potential antiparasitic agent. It was subsequently shown to possess antidepressant activity and amphetamine-like effects, but was not developed for marketing. BZP is primarily used legitimately as a chemical intermediate and is commercially available from chemical companies. BZP had been used as a treatment for internal parasites in cattle.

At the February 2003 NDPSC Meeting the Committee noted a number of emails, internet articles and abstract in relation to the abuse of BZP. Some jurisdictions advised that this substance would be appropriately controlled through Misuse of Drugs legislation and that scheduling was not necessarily the appropriate avenue of control at this time. The Committee decided not to schedule BZP at that time.

TFMPP is a piperazine-based CNS stimulant, related to BZP. TFMPP also goes by the street name of “Molly”. TFMPP is current unscheduled and has not previously come to the attention of the Committee.

DISCUSSION

Members noted that a submission had been received from XXXXXXXX regarding scheduling of BZP and TFMPP with a recommendation that, due to their misuse, these substances should be considered for inclusion in Schedule 9. The following points were considered:

- XXXXXXXX had received an enquiry expressing an interest in importing BZP from NZ. The enquirer asserted that BZP was unregulated in NZ (the Committee, however, noted the recent NZ moves to regulate drugs such as BZP, as discussed below).
- BZP was used in the party scene as an alternative to ecstasy.
- BZP was not specifically in the SUSDP, although it would be captured in Schedule 2 as a derivative of piperazine. XXXXXXXX asserted that the supply of BZP, if a Schedule 2 substance, for misuse by a person other than a pharmacist was unlikely to attract a significant penalty.
- South Australia and Western Australia included BZP and TFMPP in Schedule 9. Queensland and the Northern Territory have included BZP in their respective Misuse

of Drugs Acts. The Members also noted advice from the XXXXXXXX Member that the NT Misuse of Drugs Act lists TFMPP and other piperazine derivatives as well as BZP. XXXXXXXX asserted that a consistent approach across the States and Territories would be preferable.

- XXXXXXXX noted that the Merck Index did not include BZP and TFMPP and asserted that therefore BZP and TFMPP did not appear to be regular items of commerce in the chemical industry. The XXXXXXXX submission, however, noted that further enquiries may be needed regarding any industrial use.
- The XXXXXXXX submission also included information from the "Vaults of Erowid" website which included a number of abstracts from reputable journals and a US Drug Enforcement Administration (DEA) webpage.

The Committee considered the following information obtained from the DEA website:

- TFMPP and BZP were both given emergency controlled substance scheduling by the DEA in 2002. TFMPP was given Schedule 1 status under the Controlled Substances Act (CSA) as it had a high potential for abuse and no accepted medical use.
- A DEA webpage indicated that BZP carried substantial public health risks similar to those of amphetamine. Due to its high potential for abuse, and no accepted medical use or safety, the DEA placed BZP in Schedule I of the CSA in 2004. The Members noted that the CSA and DEA regulations permit industrial use of Schedule I controlled substances, but only under strictly regulated conditions. Additionally, the DEA website also highlighted the following:
    - Experimental studies demonstrated that the abuse, dependence potential, pharmacology, and toxicology of BZP are qualitatively similar to those of amphetamine.
    - BZP acted as a stimulant in humans and produced euphoria and cardiovascular effects, namely increases in heart rate and systolic blood pressure. BZP was about 10 to 20 times less potent than amphetamine in producing these effects. BZP was often taken in combination with other non-controlled substances in order to enhance its spectrum of effects.
    - A 2001 report from the University of Zurich, Switzerland, detailed the death of a young female attributed to the combined use of BZP and MDMA.

The Committee was advised of recent NZ steps, through changes to the *Misuse of Drugs Act* (MODA), to deal with substances such as BZP. The Members noted:

- In March 2004, the NZ Expert Advisory Committee on Drugs (EACD) recommended the creation of a new schedule for the MODA. The purpose of the new schedule was to enable some regulation for legal substances which are subject to abuse but did not warrant, on available evidence, regulation under the risk Classes A, B or C drug classifications. An example given of such a substance was BZP.

- The regulations allowed restrictions to be placed on such matters as legal age of purchase, retail, supply, marketing, and labelling in relation to substances in the new schedule.
- In June 2005, the *Misuse of Drugs Amendment Act* came into force. One outcome from this Act was the creation of the new "restricted substances" part to the legislation for controlled, but not banned, substances which included BZP.

The Committee considered a submission from XXXXXXXX opposing the scheduling of BZP and TFMPP. The Members noted the following from the submission:

- A number of harm minimization arguments including:
    - Provided a reduced risk alternative to “hard drugs”. The submission included personal and anecdotal evidence which asserted harm minimization and addiction interruption properties for BZP and TFMPP.
    - Allowed control of the purity of contents in BZP or TFMPP products.
- An argument that legal “party drug” alternatives reduced the need for criminal behaviour by otherwise law abiding citizens.
- A government revenue argument, drawing on comparisons with alcohol and tobacco. XXXXXXXX supported introduction of similar controls to those for alcohol and tobacco to be applied to BZP and TFMPP i.e. restricted to those aged 18 and over.

Members also considered a submission from XXXXXXXX opposing the scheduling of BZP. This submission:

- Echoed the above submission in asserting that BZP was a proven addiction interrupter and harm reduction aid in relation to the misuse of ecstasy and methylamphetamine.
- Asserted that use of BZP was widespread in NZ and the government there was supportive of its use in combating illegal drugs. XXXXXXXX noted that the industry in NZ was taxed and regulated and asserted that there had been no reported harm or adverse side effects from the use of BZP.
- Provided additional information from the Social Tonic Association of New Zealand (STANZ) website detailing the case put for the continuing legal use of BZP in NZ (see http://www.stanz.org.nz/documents). Documents that Members particularly considered included:
    - The *Misuse of Drugs Amendment Act 2005*, Misuse of Drugs Amendment Bill (No 3) and the Supplementary Order Paper.
    - The (STANZ) Code of Practice for the Manufacture, Labelling, Distribution and Marketing of Social Tonics in NZ.
    - A copy of the EACD advice to the NZ Minister on BZP. The Members noted that the EACD considered that:
        - It was inappropriate for BZP to be marketed as a dietary supplement.

- Regulatory options should be explored which could provide additional classifications in the Act allowing partial control, e.g. putting conditions on the promotion or sale of products, particularly to young people.
- There was reason to be concerned that evidence indicated that BZP could create adverse reactions when taken with prescription medicines, such as Selective Serotonin Re-uptake Inhibitors.
- Restricted access to products that contain BZP may lead to users of these products seeking more harmful controlled drugs as substitutes for BZP.
- There was concern over the increase in supply of these products, which were marketed and distributed independently over the internet, through counter-culture retailers, and more recently in liquor outlets, service stations and dairies in NZ. A significant industry had developed, with at least 1.5 million doses having been manufactured in NZ in 2003.
- BZP had a reported similarity to dexamphetamine and when used in combination with TFMPP had a reported effect similar to ecstasy. Although BZP was known to have a similarity of action to dexamphetamine, it was considered to be approximately ten percent of the potency.
- It was unlikely that users would attempt to match the dose strength of dexamphetamine as unwanted and unpleasant side effects were experienced at about 2 ½ times the average dose (average dose = 100 mgs BZP). The duration of action for a 100mg dose was 6/8 hours.
- One case study had been reported in which a 23 year old woman died 68 hours after ingesting BZP and 64 hours post ingestion of MDMA and a large volume of water. No linkage with the BZP was made and the death displayed all the characteristics of an ecstasy related death. She was diagnosed with cerebral oedema and with beginning tonsillar herniation. This case was considered by the DEA as evidence of BZPs potential to cause death (even though no causal links were established, the substance was implicated by its presence). Other than this one case, no other fatalities were known, therefore BZP's known potential to cause death was low, or as yet unknown.
- Use of piperazines may have the potential to start a pattern of abuse or lead to the use of more powerful illicit substances of a similar kind. Conversely, their use can reverse an abusive pattern and help avoid more powerful and harmful substances.
- Piperazine users conditioned to the effects of stimulants may more readily transfer to harmful illicit street drugs. However, there was no reported criminal behaviour associated with the use of BZP and TFMPP, as they are moderately priced and had a lower dependence potential than illicit amphetamines.

- Provided a copy of the STANZ submission to the Health Select Committee on the matter of the Misuse of Drugs Amendment Bill (No 3). This submission included a

rebuttal of the case put forward by the DEA in its restricting of BZP and an analysis of reported high profile adverse events in NZ. It also detailed the STANZ promoted industry code of practice. STANZ recommended to the NZ government the establishment of a regulatory environment that manages risk and social responsibility issues associated with social tonic use along a continuum that is commensurate with risk.

Members noted a submission from XXXXXXXX which indicated no objection to the proposed scheduling of BZP and TFMPP in Schedule 9. XXXXXXXX made the following points:

- XXXXXXXX was concerned about the way BZP had been misrepresented in the NZ market previously as a "natural dietary supplement" while being marketed as a "legal" alternative to illicit drugs. Such activities run counter to Quality Use of Medicine messages applicable to true natural-based complementary medicines and dietary supplements.

  XXXXXXXX provided an article (*Paul Gee et. al*. NZMJ, **118**, 1227) for the information of Members discussing misuse of BZP as recorded in NZ hospitals between 1 April 2005 and 1 September 2005. Members noted that the article asserted that there was a sudden escalation in presentations to the Christchurch Hospital's emergency department post 2004. The author stated that there was no human toxicity research available to help manage the overdose cases. The article included the following recommendation:

  - "Patients with seizure disorders, psychiatric illness or coronary disease should avoid BZP as should those taking prescription sympathomimetics or anticholinergics. Coingestion with MDMA or amphetamine should also be cautioned against, as this combination could lead to fatal toxicity. Users should not drive for at least 8 hours after ingesting BZP."

  The article concluded that:

  - "Many users were taking BZP-based pills without significant adverse effects. However, the results of this study indicated that BZP could cause unpredictable and serious toxicity in some individuals. BZP is currently a legal stimulant in NZ and this status makes it available and attractive to a far wider market of users than if it were illicit. Moreover, it has propagated a culture of accepting pill use as a normal behaviour at parties. These factors should be carefully weighted in any consideration of the legal status of piperazine-based party pills".

The Committee noted a submission from XXXXXXXX which advised that it had checked to establish if either BZP or TFMPP were used in legitimate domestic products. The XXXXXXXX advised that no such use was discovered.

The XXXXXXXX Member asserted that this issue was similar to that concerning gammabutylactone (GBL). The Member noted:

- In jurisdictions such as XXXXXXXX where the drugs and poisons legislation and the misuse of drugs legislation are separate, the need to include drug precursors in the SUSDP schedules was not an issue.
- However, certain jurisdictions required scheduling to ensure access to precursors was restricted. The Member recalled that GBL was included in Schedule 7 to enable those jurisdictions with controlled substances legislation to issue permits to control the legitimate use of the substance.
- The Member advised that XXXXXXXX would be happy for BPZ and TFMPP to remain unscheduled and use the misuse of drugs legislation to deal with inappropriate use. However, this would obviously not satisfy the requirements of jurisdictions that do not have controlled substances legislation.

Members also considered advice from the XXXXXXXX Member which noted:

- That BZP and TFMPP were currently not regulated in Victoria.
- XXXXXXXX had little information to suggest that there was an abuse problem.
- XXXXXXXX also do not suggest a major problem.
- It would appear that listing in Schedule 9 would have little impact on legitimate use, if any.

The Members also considered a submission from XXXXXXXX. XXXXXXXX indicated:

- It had sought advice from member companies regarding information on the legitimate industrial uses of BZP and TFMPP, and had not received any information to indicate these substances were currently being used by XXXXXXXX members.
- It was, however, aware that piperazine (a building block for piperazine derivatives) did have uses in industry e.g. it was used in CO_2 removal in ammonia production.
- If the NDPSC considers BZP and TFMPP should be included in the PACIA/Science Industry Australia Code of Practice on Supply Diversion into Illicit Drug Manufacture (the Code), XXXXXXXX would be happy to address this matter in discussion with the XXXXXXXX. Members recalled that this would be consistent with the outcome of the June 2003 NDPSC Meeting at which the Committee recommended that GHB, its precursors and analogues be included in the Code. However, Members noted that the purpose of the Code was primarily for drug precursors and end user declarations. BZP and TFMPP, as end user drugs which would most likely be imported, would not be controlled appropriately through inclusion in the PACIA Code of Conduct.

Members were advised that a Secretariat search of PUBCRIS located no reference to any products containing BZP although it appeared to be used in some worming tablets in New Zealand (NZ).

Members were also advised that the piperazine ring and piperazine derivatives are important cyclic components in industry as raw materials for hardeners of epoxy resins, corrosion inhibitors, insecticides, accelerators for rubber, urethane catalysts and antioxidants. The Committee noted a list of some commercial suppliers for BZP and TFMPP and generally agreed that there was no current industrial use in Australia that would be inadvertently impacted by scheduling of BZP and TFMPP.

DECISION 2006/46 - 36

The Committee agreed, due to abuse potential, to include benzylpiperazine and 1-(3-trifluoromethylphenyl)piperazine in Schedule 9.

Schedule 9 – New entries

BENZYLPIPERAZINE *(BZP).

1-(3-TRIFLUOROMETHYLPHENYL)PIPERAZINE *(TFMPP).

15. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

15.1 FLUCONAZOLE

PURPOSE

The Committee considered the Appendix F Warning Statements and Appendix H entry for fluconazole.

BACKGROUND

Fluconazole is a triazole antifungal drug that, in sensitive fungi, inhibits cytochrome P450-dependant enzymes resulting in impairment of ergosterol synthesis in fungal cell membranes. Fluconazole is active against *Blastomyces dermatitidis*, Candida spp., *Coccidioides immitis*, *Cryptococcus neoformans*, Epidermophyton spp., *Histoplasma capsulatum*, Microsporum spp., and Trichophyton spp.

Fluconazole is used to treat superficial mucosal (oropharyngeal, oesophageal or vaginal) candidiasis and fungal skin infections. It is also used for systemic infections including systemic candidiasis, coccidioidomycosis and cryptococcosis. Resistance has developed in some Candida spp. following long-term prophylaxis with fluconazole, and cross-resistance with other azoles has been reported. Dosage is given by mouth or intravenous infusion in similar doses.

Fluconazole was first considered for scheduling at the August 1991 NDPSC Meeting where it was included in Schedule 4 of the SUSDP. At the June 2003 NDPSC Meeting

the Committee agreed to include fluconazole in Schedule 3 for single-dose oral preparations containing 150 mg for the treatment of vaginal candidiasis. This decision was made on the basis of its similar safety profile to topically applied antifungal agents, and was considered appropriate for similar Schedule 3 availability.

At the October 2003 NDPSC Meeting the Committee agreed to vary the June 2003 NDPSC Meeting Decision to include fluconazole in Appendix F and Appendix H of the SUSDP. Members agreed that inclusion in Appendix F (Warning Statement 64 (WS 64)) and Appendix H was consistent with other Schedule 3 imidazole antifungals for vaginal use, these including clotrimazole, econazole and miconazole.

> WS 64 currently reads:
>
> 64. See a doctor (or) (dentist) if no better after (Insert number of days as per approved Product Information) days.

In 2003, MEC set a period of "three days" for incorporation into WS 64 for fluconazole as the vaginal mucosa would not necessarily have recovered earlier than this after a single dose fluconazole treatment.

The fluconazole scheduling amendments came into effect on 1 January 2004.

DISCUSSION

Appendix H

Members noted the recommendation from the August 2005 MEC Meeting that the NDPSC be asked to remove fluconazole from Appendix H of the SUSDP to avoid advertising pressure that would make it more difficult for pharmacists to exercise their professional discretion in recommending the use of an oral or topical treatment for vaginal candidiasis. The MEC was concerned that advertising of Schedule 3 products containing fluconazole directly to consumers may increase the likelihood of excessive or inappropriate use, and may mean that consumers, particularly those on low incomes and/or from non-English speaking backgrounds, are not aware of the availability of cheaper (topical) treatments for vaginal candidiasis. The MEC also agreed to change the ARTG indications from "Treatment of vaginal candidiasis when topical therapy has failed" to "Treatment of vaginal candidiasis", in response to the sponsor's request to redefine fluconazole to an alternative first-line treatment for vaginal candidiasis from the existing second-line treatment status.

Members noted that fluconazole 150 mg could be advertised direct to the consumer with restricted representations. The TGA required that advertisements do not imply the use of Diflucan One as an alternative to topical therapy for vaginal candidiasis and that they make it clear that its use is only appropriate after topical therapy has been found to be ineffective in every outbreak of vaginal candidiasis. With the change to the ARTG

indications for fluconazole 150 mg to "treatment of vaginal candidiasis" it is likely that direct to consumer advertising would be allowed without restrictions.

Members considered submissions received from XXXXXXXX, XXXXXXXX and XXXXXXXX, all supporting the continued inclusion of fluconazole in Appendix H. XXXXXXXX disagreed with the MEC's recommendation regarding the Appendix H status for fluconazole and the concerns raised by MEC that consumer may "not be aware of the availability of cheaper (topical) treatments for vaginal candidiasis"; that advertising would increase "the likelihood of excessive or inappropriate use"; and "advertising pressure that would make it more difficult for pharmacists to exercise their professional discretion". It is asserted by XXXXXXXX that there is no evidence that advertising of fluconazole to consumers is likely to lead to misuse, overuse or other safety concerns, and removal of fluconazole from Appendix H would create an inequitable marketing environment between fluconazole and other azole antifungals. It was emphasized by XXXXXXXX that any advertising of an S3 product is required by the Therapeutic Goods Advertising Code to include specific statements that a pharmacist's advice is required with regard to choice of that product, and the advertising does not impact the professional skills and ability of the pharmacist to offer appropriate advice and supervision.

Members recalled that the October 2003 NDPSC Meeting agreed to include fluconazole in Appendix H when it was included in Schedule 3, given that there should be reinforcement through appropriate advertising that the product was recommended as a second-line treatment for vaginal candidiasis after the failure of a topical antifungal. While second-line treatments usually require consultation with a doctor or pharmacist to rule out other causes of the patient's symptoms and to minimise the chance of misdiagnosis, the Committee considered that women would be able to readily identify a vaginal candidiasis infection not responding to topical treatment. Furthermore, the Committee believed that the pharmacist is well placed to provide professional advice on available pharmacotherapy options for vaginal candidiasis in the event that the first-line topical treatment had failed. Members also recalled the following points highlighted at the October 2003 NDPSC Meeting:

- Comparable vaginally applied treatments for the same condition are permitted to be advertised, and alerting women to the availability of an alternative orally administered product could be considered a useful public health message.
- The sponsor committed to adhere to the Therapeutic Goods Advertising Code, to include the importance of initial medical diagnosis and the pharmacists' counselling role, and provide CMI and other material needed to educate product users.
- Low potential for advertising to promote inappropriate use.

The Committee noted that no particular public health concerns had arisen based on the marketing experience over the past couple of years with fluconazole 150 mg available as a "Pharmacist Only" medicine and able to be advertised directly to consumers. The Committee was of the view that the slight change in the indication for fluconazole 150

mg, i.e. from the current second-line treatment status to an alternative first-line treatment for vaginal candidiasis, was unlikely to impact adversely on its safety profile.

Appendix F

Members were informed by the Secretariat that an enquiry was received from XXXXXXXX of the TGA regarding the Appendix F entry for fluconazole. The Committee noted the following points:

- XXXXXXXX enquiry was - since the fluconazole entry in Appendix F does not specify the fluconazole Schedule, does this mean that Schedule 4 oral fluconazole would also require WS 64 on the product label?
- XXXXXXXX noted that *Required Advisory Statements for Medicine Labels* (RASML), in reflecting the SUSDP, has consequently also mandated a RASML warning statement for fluconazole in any SUSDP schedule.
- XXXXXXXX also noted that following the June 2003 NDPSC Meeting the MEC considered the fluconazole decision. Part of the MEC's decision was agreement that if the NDPSC proceeds to include fluconazole in Schedule 3 (in single-dose oral preparations containing 150 mg or less of fluconazole for the treatment of vaginal candidiasis), Appendix F WS 64 should be required for these products.
- OTC advised that the RASML would only be updated to reflect this if the NDPSC amended Appendix F.
- The Secretariat advised XXXXXXXX that it appeared that it was an oversight at the October 2003 NDPSC Meeting not to specify in the Appendix F entry that WS 64 was only required for Schedule 3 oral fluconazole intended for the treatment of vaginal candidiasis

The submission by XXXXXXXX also opposed to the proposal to apply an Appendix F Warning Statement to Schedule 3 fluconazole, and asserts that the current precautions and advisory statements on the label are sufficient.

Members noted that in the June and October 2003 NDPSC Meetings, other S3 substances for vaginal use such as clotrimazole, econazole and miconazole were also included in Appendix F and required to be labelled with WS 64. The Appendix F entry for these pharmaceuticals includes the statement "…in vaginal preparations when included in Schedule 3". Hence, similar wording should also be included in the Appendix F entry for fluconazole.

DECISION 2006/46 - 37

The Committee confirmed that the current Appendix H entry for fluconazole remains appropriate. The Committee also agreed that for the fluconazole entry in Appendix F,

warning statement 64 was only required for a product included in Schedule 3 and supported a change to the fluconazole Appendix F entry to reflect this position.

Appendix F, Part 3 – Amendment

Fluconazole – Amend entry to read

POISON	**WARNING STATEMENT**
Fluconazole in oral preparations when included in Schedule 3.	64

15.2 IBUPROFEN

PURPOSE

The Committee considered an amendment to confirm its intent that solid dose ibuprofen products (less than 200mg per dosage unit) labelled for use in children aged 6 years and under should be included in Schedule 2.

BACKGROUND

In response to the recommendations of the Review of non-prescription analgesic – An update which was released by the Medicines Evaluation Committee (MEC) in April 2003, the June 2003 NDPSC meeting commenced a review of label requirements for non-prescription analgesics including NSAIDs, which took several meetings to finalise.

The June and October 2003 meetings agreed to exempt appropriately labelled small packs of oral ibuprofen 200mg from the requirements of scheduling.

The October 2005 NDPSC meeting amended the S2 entry for ibuprofen to transfer the warning statements to the *Required Advisory Statements for Medicine Labels* (RASML).

DISCUSSION

[Sentence deleted**]**

The Committee noted a submission from the MEC seeking an amendment to the S2 entry for ibuprofen. The issue was raised in the MEC meeting on 6 October 2005 when an application was considered for registration of a chewable tablet containing 100 mg ibuprofen which is intended for use in children aged 2 to 12 years. The proposed labelling presented the tablets as an unscheduled product. The MEC noted that the current SUSDP Schedule 2 entry for ibuprofen indicates that ibuprofen is exempt from scheduling in divided preparations each containing 200 mg or less of ibuprofen as the only active

ingredient, with a recommended daily dose of 1200 mg or less, in blister or strip packaging or in a container with a child resistant closure, and in packs of 25 or less tablets, provided the labelling includes warnings consistent with SUSDP Appendix F warning statements (WS) 101 and 104, plus the following additions to WS 104:

Unless your doctor has told you to, don't use [this product / name of product]:
- In children 6 years of age or less;
- If you are aged 65 years or over.

Members noted the inconsistencies between the scheduling of products containing ibuprofen and paracetamol, i.e. that solid dose products containing ibuprofen can be exempt from scheduling, with no age limit, provided the relevant label warnings are included and the product meets other specified requirements, whereas paracetamol products labelled for use in children aged 6 years or under are in Schedule 2.

Members discussed MEC's advice regarding amending the Schedule 2 entry for ibuprofen to remove the exemption for solid-dose products labelled for use in children aged 6 years or under. Some members expressed the view that this would be a significant change for ibuprofen scheduling, and needed to be discussed separately, and it should not be automatically included just for consistency with paracetamol. A member indicated that there were a number of existing ibuprofen products in the market which might be affected by the potential change.

OUTCOME

Accordingly, the Committee agreed to foreshadow a decision to amend the Schedule 2 entry for ibuprofen to remove the unintentional exemption for solid-dose products labelled for use in children aged 6 years or under. The item will be gazetted for public comment to allow consideration of the matter at the June 2006 meeting.

FORESHADOWED DECISION (for consideration at the June 2006 meeting)

Schedule 2 – Amendment

IBUPROFEN – Amend entry to read:

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

(a) in liquid preparations when sold in the manufacturer's original pack containing 4 grams or less of ibuprofen; or

(b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:

(i) as the only therapeutically active constituent other than an effervescent agent;

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

(iii) in a primary pack containing not more than 25 dosage units;

(iv) not labelled for the treatment of children 6 years of age or less; and

(v) complies with the requirements of the *Required Advisory Statements for Medicine Labels.*

16. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

16.1 NOVEMBER 2004 AND JUNE 2005 MCC MEETINGS

16.1.1 NASAL CORTICOSTEROID PREPARATIONS (FLUTICASONE, BECLOMETHASONE, BUDESONIDE, MOMETASONE AND TRIAMCINOLONE)

PURPOSE

The Committee considered the MCC and TTHWP recommendations to harmonise the scheduling of nasal corticosteroids in S2 with New Zealand.

BACKGROUND

The October 2005 NDPSC meeting considered the recommendations of the November 2004 and June 2005 MCC meetings as well as the outcomes of the TTHWP Meeting 14 (10 October 2005) in relation to the following substances:

- Fluticasone: The June 2005 MCC meeting recommended that Australia adopt the New Zealand maximum daily dose limit of 200 µg of fluticasone in S2. The MCC was of the view that fluticasone was twice as potent as the other nasal corticosteroids and that it was appropriate that the dose limit in S2 reflect this accordingly.
- Triamcinolone, Beclomethasone, Budesonide and Mometasone: The Committee noted that the S2 entries for these substances were not fully harmonised due to differences in dosage and pack size restrictions and the conditions specified for products in S2. To harmonise the S2 and Part III entries, the Committee agreed with the TTHWP proposal that the NDPSC should recommend to MCC to consider

adopting the condition “for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over” in Part III. Furthermore, in order to fully harmonise the S2 and Part III entries, the Committee also agreed with the TTHWP proposal to remove the pack size restriction specified for all corticosteroid nasal sprays in S2 for consistency across the class. This would be consistent with the approach agreed for beclomethasone and budesonide discussed under item 1.8.1.2 (1.8.1.2.8 beclomethasone and budesonide).

DISCUSSION

A member advised that the scheduling condition "for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over" was already included in the regulatory guidelines for the approval of OTC nasal corticosteroid preparations in New Zealand and therefore was not expected to have any additional regulatory impact on existing products in New Zealand. Members noted that the October 2005 NDPSC meeting already forwarded this recommendation to MCC for consideration as part of the outcomes of that meeting.

The same member also stated that New Zealand was already harmonised with Australia on the pack size restriction of 200 actuations or less and that this was specified in New Zealand’s registration guidelines. The member noted that the only issue left to consider was the need to retain the pack size restriction given that the duration of treatment of allergic rhinitis for up to 6 months was also specified in the S2/Part III entries for all nasal corticosteroids.

Members were advised that the issue of pack size restriction was also discussed under agenda item 1.8.1.2 (1.8.1.2.8 beclomethasone and budesonide) and that the deletion of the pack size restriction had been accepted by the Committee and incorporated into the amendments foreshadowed at the October 2005 NDPSC meeting.

The Committee noted the XXXXXXXX pre-meeting submission which indicated that a dose of 250 micrograms of fluticasone is equivalent to 400 micrograms beclomethasone (non-CFC formulation) and budesonide.

DECISION 2006/46 - 38

The Committee agreed to amend the S2 entries for fluticasone, beclomethasone, budesonide, mometasone and triamcinolone and harmonise the scheduling of these substances with New Zealand. Furthermore, the Committee agreed to adopt the New Zealand maximum daily dose limit of 200 µg for fluticasone in S2 to harmonise with New Zealand.

Schedule 2 – Amendments

BECLOMETHASONE – amend entry to read:

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 for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

BUDESONIDE – amend entry to read:

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 for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

FLUTICASONE – amend entry to read:

FLUTICASONE in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 200 micrograms for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

MOMETASONE – amend entry to read:

MOMETASONE in aqueous nasal sprays delivering 50 micrograms or less of mometasone per actuation when the maximum recommended daily dose is no greater than 200 micrograms for the prophylaxis or treatment of allergic rhinitis for up to six months in adults and children 12 years of age and over.

TRIAMCINOLONE – amend entry to read:

TRIAMCINOLONE in aqueous nasal sprays delivering 50 micrograms or less of triamcinolone per actuation when the maximum recommended daily dose is no greater than 200 micrograms for prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

16.1.2 MEPYRAMINE, OXICONAZOLE AND SCHOENOCAULON OFFICINALE (SABADILLA)

PURPOSE

The Committee considered recommendations from the November 2004 and June 2005 MCC meetings and October 2005 TTHWP meeting in relation to the substances below.

16.1.2.1 MEPYRAMINE

BACKGROUND

Mepyramine, an ethylenediamine derivative, is a sedating antihistamine with antimuscarinic and sedative properties. Mepyramine maleate is used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders. Mepyramine maleate is also a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold.

As part of the TTHWP recommendations, the February 2005 NDPSC meeting agreed to foreshadow harmonisation with the New Zealand scheduling for mepyramine. To achieve this, the NDPSC foreshadowed to delete the S3 entry for oral preparations, reschedule dermal preparations from S4 to S2 and make consequential amendments to the S4 entry.

However, the June 2005 NDPSC pre-meeting gazette notice advised the intent to consider the scheduling of mepyramine being one of the substances identified in the SUSDP where there were no Schedule 2 or Schedule 3 products in the marketplace. On this basis, all preparations containing mepyramine were to be considered for rescheduling to S4 on the basis of an agreed policy approach. This policy approach was agreed by the April 2005 NCCTG meeting (68th Meeting) for dealing with the harmonisation of S2 or S3 substances where no products containing these substances are being marketed in either Australia or New Zealand. NCCTG agreed to the NDPSC's proposal that such S2 and/or S3 entries in the SUSDP should be deleted and the parent compounds be added or retained in S4 of the SUSDP. The June 2005 NDPSC meeting noted that to allow dermal use of products containing mepyramine would be inconsistent with the NDPSC policy of not permitting the dermal use of sensitizing antihistamines. The Committee therefore agreed not to align the Schedule 2 classification of mepyramine for dermal use with New Zealand. Also, as it was believed that there were no oral preparations of mepyramine registered in Australia, the Committee recommended the deletion of mepyramine for oral use from Schedule 3 and reflect consequential amendments in the S4 entry. It was noted that New Zealand had one registered topical Pharmacy Only product in the SMARTI database and the NDPSC recommended that MCC reconsider the availability of mepyramine dermal preparations as pharmacy medicines given the concerns on sensitisation.

The October 2005 NDPSC meeting was advised that the decision made at the June 2005 NDPSC meeting to remove mepyramine in oral preparations from Schedule 3 was based on incorrect information that there were no products in Australia when in reality there was one oral product (3 different volumes) registered on the ARTG containing mepyramine for supply in Australia. The October 2005 NDPSC meeting also noted that the June 2005 MCC meeting stated that the sensitisation issue with mepyramine was not a widespread problem in New Zealand and that its safety profile was comparable to local anaesthetics which had remained available as OTC medicines in New Zealand. On this basis, the MCC agreed that a more restrictive scheduling to harmonise with Australia was

not warranted at this time and recommended that the NDPSC consider harmonisation with the New Zealand scheduling of mepyramine.

DISCUSSION

The Committee noted that to fully harmonise the scheduling of mepyramine, two issues needed to be addressed: harmonisation with the New Zealand Pharmacy Only classification for topical preparations and harmonisation with the SUSDP S3 classification for oral preparations, both of which were least restrictive scheduling. It was pointed out that New Zealand did not have a Restricted Medicine entry for mepyramine therefore oral preparations were classified prescription medicines. Members noted that this harmonisation proposal took into account the dermal product in New Zealand and the oral products in Australia.

The Committee noted that advice was sought from the Adverse Drug Reactions Unit (ADRU) on adverse reaction reports on mepyramine but there were none reported in Australia although this could be more likely due to the absence of products on the market. Information on adverse reports in New Zealand was also sought and it was advised that two reports involving topical mepyramine were received. The first was XXXXXXXX which was used topically for two weeks and resulted in an acute exudative eczema. This report was received in 1971 and was the only report for XXXXXXXX. The second report was received in March 1978 and related to XXXXXXXX which contained at that time phenazone, phenylephrine and mepyramine. The reaction was a 'local allergy'. The existing XXXXXXXX formulation contained phenylephrine hydrochloride 0.12% and polyvinyl alcohol 1.4% and benzalkonium chloride. Furthermore, members noted a summary from the WHO database which showed 44 reports relating to mepyramine over a period of approximately 35 years demonstrating the substance's good safety record.

Members were informed that the TGA's advice in relation to the issue of sensitisation from topical mepyramine stated that the current version of Therapeutic Guidelines - Dermatology Version 2, 2004 had touched on the subject of antihistamines for their sedating effects but no mention was made of topical antihistamines. On this basis, the Committee concluded that the concern on topical mepyramine causing skin sensitisation was unlikely to be a significant issue at this time.

The Committee noted XXXXXXXX pre-meeting submission expressing support for the harmonisation of scheduling of mepyramine with New Zealand.

DECISION 2006/46 - 39

The Committee agreed to harmonise with New Zealand and adopt the S2 entry for mepyramine for dermal use. Similarly, the Committee agreed to recommend that New Zealand adopt the S3 entry for mepyramine in oral preparations to fully harmonise the scheduling of mepyramine.

Schedule 2 – New entry

MEPYRAMINE for dermal use.

Schedule 4 – Amendments

MEPYRAMINE – amend entry to read:

MEPYRAMINE **except** when included in Schedule 2 or 3.

16.1.2.2 OXICONAZOLE

BACKGROUND

The June 2005 NDPSC meeting agreed to exempt from the requirements of scheduling all antifungal preparations including oxiconazole for the treatment of *tinea pedis* to harmonise with New Zealand and amended the S4 entry for oxiconazole accordingly. The June 2005 MCC Meeting noted the NDPSC's decision to exempt antifungal preparations for the treatment of *tinea pedis* and further recommended that Australia harmonise fully with the New Zealand classification for oxiconazole and reschedule this medicine from S4 to OTC availability (S2, S3 and General Sale). The MCC recommendation was based on the three products on the New Zealand database which had been granted consent to market as Pharmacy Only medicines. In addition, MCC pointed out that rescheduling oxiconazole to OTC level in Australia would be consistent with the scheduling of most antifungal agents in the SUSDP.

DISCUSSION

Members were advised that there were no products containing oxiconazole on the ARTG and none of the three products approved in New Zealand in the early '90s had been marketed according to SMARTI.

Members noted that the June 2005 MCC meeting's observation that the scheduling of oxiconazole products as non-prescription medicines would be consistent with most other antifungals in the SUSDP was not entirely correct in that all antifungal agents in S2 and S3 have parent entries in S4, i.e. clotrimazole, fluconazole, isoconazole, miconazole and sulconazole. On this basis, members considered that whilst the aim of Trans-Tasman Harmonisation is to harmonise on the least restrictive scheduling, deleting the S4 entry for oxiconazole and rescheduling the substance to S2 and S3 to harmonise with the New Zealand classification may not be appropriate from a public health perspective given the lack of clinical experience with oxiconazole in both countries. Members noted that none of the three Pharmacy Only products approved in New Zealand in the early '90s appeared to have ever been marketed. Furthermore, members contended that New Zealand's lack of a Prescription Medicine entry for oxiconazole may be an oversight since all the

antifungal agents in S2 and S3 of the SUSDP cited above had corresponding parent entries in S4 in New Zealand. Therefore, it was suggested that it may be appropriate to recommend that MCC consider including in Part I an entry for oxiconazole for consistency with the other antifungal medicines included in the New Zealand schedules.

Members noted the pre-meeting submission received from XXXXXXXX expressing support for harmonisation of the scheduling of oxiconazole with New Zealand.

A member advised that when New Zealand reclassified all antifungals to move preparations for the treatment of *tinea pedis* to General Sale, an entry for oxiconazole for vaginal use was also created in Part II (S3) for consistency with the entries of other antifungal agents, even when there was no registered product. The member suggested that New Zealand would support the inclusion of a Prescription Medicine entry for oxiconazole for consistency with other antifungals but argued against deleting the non-prescription entries for oxiconazole and rescheduling all preparations to Prescription Medicine. The Member stated that irrespective of the fact that the products on the SMARTI database had never been marketed, the registration status for such products had remained active and on this basis, these products could be launched on the market at any time. On this basis, the member proposed that the Committee consider harmonising with the New Zealand S2 and S3 entry for oxiconazole and recognising that there was significant experience already in place in Australia with other imidazole antifungals and the member expected the safety profile of oxiconazole to be similar to the other antifungals of this class.

DECISION 2006/46 - 40

The Committee agreed that the safety profile of oxiconazole was expected to be similar to other imidazoles which have a long history of safe use in Australia. On this basis, the Committee agreed to adopt the S2 and S3 entries for oxiconazole. Similarly, the Committee agreed to recommend that New Zealand adopt an S4 entry for oxiconazole to fully harmonise the scheduling of oxiconazole.

Schedule 2 – New entry

OXICONAZOLE for dermal use **except** in preparations for the treatment of tinea pedis.

Schedule 3 – New entry

OXICONAZOLE in preparations for vaginal use.

Schedule 4 – Amendment

OXICONAZOLE – amend entry to read:

OXICONAZOLE **except**:

(a) when included in Schedule 2 or 3; or

(b) in preparations for the treatment of tinea pedis.

16.1.2.3 SCHOENOCAULON OFFICINALE (SABADILLA)

BACKGROUND

The October 2005 NDPSC meeting noted that the MCC June 2005 meeting recommended that Australia harmonise with the New Zealand scheduling of sabadilla which was reclassified to permit the continued sale of complementary products that were already on the market. The MCC also indicated that the material it had reviewed to support reclassification in New Zealand would be forwarded to the NDPSC for consideration at the February 2006 meeting.

CONSIDERATIONS

The Committee noted that New Zealand had provided a copy of XXXXXXXX submission in relation to Sabadilla which was considered by the MCC.

The Committee was informed that comment was sought from OCM on the proposal to harmonise with the New Zealand classification for sabadilla and in addition, XXXXXXXX submission to MCC, which formed the basis of the current scheduling of sabadilla in New Zealand, was also forwarded to OCM for comment. The Committee noted the following points raised in OCM's advice:

- The OCM agrees with the principle of the MCC proposed scheduling being based on the total alkaloids (the known toxic component) of *Schoenocaulon officinale*.
- With regard to XXXXXXXX submission for reclassification of Sabadilla, the OCM considers that there is not enough information to provide an informed opinion on appropriate safety levels for the alkaloids of Sabadilla. In particular, the OCM questions XXXXXXXX how the Lethal Dose of 180 mg was determined and, also, questions the justification of 5-20 grains as a 'therapeutic dose'. In addition, as a NOEL does not appear available, a safe long term intake cannot be determined.
- In the absence of a suitable safety evaluation being undertaken for *Schoenocaulon officinale*, the OCM cannot provide an informed comment on the limits applied for the proposed scheduling of this substance.

It was noted that a search of the SMARTI database yielded one prescription medicine sponsored by XXXXXXXX containing multiple ingredients including sabadilla at 6x. OCM had also advised that there were 8 homoeopathic medicines listed on the ARTG with *Schoenocaulon officinale* as an ingredient (in potencies ranging from 2 X to 6 X in multi-ingredient formulations). However, members noted that no information on

sabadilla's clinical use was available from the XXXXXXXX submission and OCM's advice did not include a discussion of the approved indications in Australia.

A member advised that one homeopathy site on the internet (http://www.abchomeopathy.com/r.php/Sabad) suggested that sabadilla was being used as an ingredient in homeopathic preparations for the treatment of a wide range of symptoms including hayfever, wet nose, cough, chills and fever.

The Committee expressed a view that it would be inappropriate to allow the substance outside of S4 on the basis of the advice received from OCM that in the absence of a safety evaluation the Office could not make an informed comment on the proposal to allow the General Sale and S2 availability of sabadilla to harmonise with New Zealand.

Members argued that since sabadilla is an approved ingredient in Listed medicines, the safety of the substance used in homeopathic preparations must have already been assessed by CMEC. In addition, new S2 medicines containing sabadilla would be subject to OTC evaluation at registration and should address the safety and efficacy of this substance.

XXXXXXXX reminded members that the Committee did not have adequate evidence to support a decision to harmonise with New Zealand based on the requirements of section 52 E of the Therapeutic Goods Act 1989 (the Act), particularly in relation to the safety of the substance.

The Committee noted that XXXXXXXX pre-meeting submission had asked to be allowed to comment on the outcome of the Committee's consideration of this matter.

OUTCOME

The Committee concurred with OCM's advice that a safety evaluation was required to make an informed judgment on the limits to be applied for the proposed scheduling of sabadilla, if appropriate. On this basis, the Committee agreed to defer consideration of this matter to the June 2006 meeting and seek advice from the OCM on the safe and appropriate concentration limits to be applied to S2 and exempt preparations.

16.1.3 NEW S4 MEDICINES (FULVESTRANT, PALONOSETRON, TERLIPRESSIN, ALEMTUZUMAB, ANECORTAVE, ENTECAVIR, ERLOTINIB, MURAGLITAZAR, NESIRITIDE, PEGAPTANIB, POSACONAZOLE AND SOLIFENACIN)

PURPOSE

The Committee considered the inclusion in Schedule 4 (S4) of new medicines classified in New Zealand as Prescription Medicines.

BACKGROUND

The November 2004 MCC meeting agreed to classify the new medicines below, i.e. fulvestrant, palonosetron and terlipressin, as Prescription Medicines. Accordingly, the October 2005 NDPSC meeting agreed to foreshadow their inclusion in S4 to harmonise with New Zealand. The following information were considered by MCC:

- **Fulvestrant XXXXXXXX solution for injection.**

Fulvestrant is an oestrogen receptor antagonist that blocks the action of oestrogen and is associated with down-regulation of the oestrogen receptor protein. It is described as an Oestrogen Receptor Downregulator. It blocks the trophic action of oestrogens without eliciting any agonist action, either on the tumour tissue or on other tissues. Fulvestrant binds to oestrogen receptors in a competitive manner with a high affinity comparable to that for oestradiol.

The proposed indication is for the treatment of postmenopausal women of any age with locally advanced or metastatic breast cancer who have been previously treated with endocrine therapy, irrespective of whether their postmenopausal status occurred naturally or was artificially induced.

- **Palonosetron hydrochloride XXXXXXXX solution for injection**.

XXXXXXXX is a highly selective 5-HT antagonist. It is an antiemetic and antinauseant agent. It is a selective serotonin subtype ($5HT_3$) antagonist with a strong binding affinity for this receptor. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5HT receptors located on vagal afferents to initiate the vomiting reflex.

The proposed indications are for:

1. the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer therapy and
2. the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

- **Terlipressin XXXXXXXX powder for injection.**

Terlipressin may be regarded as a circulating depot of lysine vasopressin. Following intravenous injection, terlipressin has an initial effect of its own, and then the three glycyl moieties are enzymatically cleaved from the N-terminus to release lysine vasopressin. The slowly released vasopressin reduces blood flow in the splanchnic circulation in a prolonged manner, thereby helping to control bleeding from ruptured oesophageal varices.

The proposed indication is for the treatment of bleeding oesophageal varices.

The June 2005 MCC meeting agreed to classify the new medicines below, i.e. alemtuzumab, anecortave, entecavir, erlotinib, muraglitazar, nesiritide, pegaptanib,

posaconazole and solifenacin, as Prescription Medicines. Accordingly, the October 2005 NDPSC meeting agreed to foreshadow their inclusion in S4 to harmonise with New Zealand. The following information was considered by MCC.

- **Alemtuzumab XXXXXXXX concentrate for infusion.**

Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface gylcoprotein (CD52) expressed primarily on the surface of normal and malignant peripheral blood B and T cell lymphocytes. It causes the lysis of lymphocytes by binding to CD52, a highly expressed, non-modulating antigen which is present on the surface of essentially all B and T cell lymphocytes, as well as monocytes and macrophages. The antibody mediates the lysis of lymphocytes via complement fixation and antibody dependent cell mediated cytotoxicity. The antigen has been found on a small percentage of granulocytes, but not on erythrocytes or platelets. Alemtuzumab does not appear to damage haematopoietic stem cells or progenitor cells.

The proposed indication is for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have been treated with alkylating agents and who have failed to achieve a complete or partial response or achieved only a short remission (less than six months) following fludarabine phosphate therapy.

- **Anecortave acetate XXXXXXXX depot suspension injection**.

Anecortave acetate is a unique angiostatic agent that may represent a breakthrough in the therapy of ocular neovascular diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. Anecortave acetate is derived from cortisol with specific and permanent changes to the original cortisol structure resulting in the creation of an angiostatic "cortisene" which does not exhibit typical glucocorticoid receptor-mediated activity *in vivo*, neither non-clinically or clinically. The body of non-clinical evidence indicates that anecortave acetate inhibits subfoveal neovascularisation and lesions that cause vision loss. It has been shown to be an effective inhibitor of angiogenesis by blocking vascular endothelial cell proliferation and the synthesis of proteolytic enzymes that cause new vessel growth.

The proposed indication is for the treatment of exudative age-related macular degeneration.

The registration of XXXXXXXX injection suspension containing 15 mg/0.5mL of anecortave acetate has been approved by the TGA but the substances is not currently listed in the SUSDP.

- **Entecavir (XXXXXXXX) tablets and oral solution.**

Entecavir is a guanosine nucleoside analogue with selective activity against hepatitis V virus. It is a selective polymerase inhibitor for HBV. Its intrinsic potency against HBV in vitro is 300 to 1400-fold greater than lamuvidine. Potency contributes to a

favourable resistance profile particularly in nucleoside-naïve patients, where resistance emergence was not reported.

The proposed indication is for the treatment of chronic HBV infection in adults with evidence of active liver inflammation.

- **Erlotinib hydrochloride (XXXXXXXX) film coated tablets.**

Erlotinib is a small molecule designed to target the human epidermal growth factor receptor type 1 (HER1) pathway, which is one of the factors critical to cell growth in many cancers. HER1, also known as EGFR is a key component of the HER signalling pathway, which plays a role in the formation and growth of numerous cancers. XXXXXXXX is designed to inhibit the tyrosine kinase activity of the HER1 signalling pathway inside the cell, which may block tumour cell growth.

The proposed indication is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received chemotherapy.

- **Muraglitazar tablets.**

Muraglitazar is the first in a new class of oral antidiabetic agents, the glitazars. It is a potent dual acting agonist of peroxisome proliferators-activated receptor gamma (PPARγ) and peroxisome proliferators-activated receptor alpha (PPARα).

Muraglitazar has also been shown to significantly lower triglycerides and increase HDL-cholesterol while having a neutral effect on LDL-cholesterol.

The proposed indication is for use as an adjunct to diet and exercise to improve glycaemic control and diabetic dyslipidaemia in patients with type 2 diabetes.

- **Nesiritide (rbe) XXXXXXXX powder for injection.**

Nesiritide is a recombinant version of human B-type natriuretic peptide (hBNP) and has the same amino acid sequence as endogenous hBNP.

Nesiritide has a direct vasodilatory effect on both arterial and venous vessels and inhibits endothelial cell release of the vasoconstrictive peptide endothelin-1. It also stimulates sustained diuresis and natriuresis (potassium sparingly) by increasing the glomerular filtration rate, and inhibiting sodium and water reabsorption in the distal tubules of the kidneys, both directly, and via a reduction in rennin and aldosterone levels. Nesiritide is believed to exert most of its biological actions by activating the guanylyl cyclase-A (GC-A) receptor which is found on the surface of endothelial and smooth muscle cells. Binding of nesiritide to the GC-A receptor results in the synthesis and intracellular accumulation of cyclic GMP. By acting as a second messenger, cyclic GMP appears to mediate most, if not all, of the biological effects of nesiritide.

The proposed indication is for the treatment of patients with decompensated congestive heart failure (DCHF) who have dyspnoea at rest or with minimal activity.

- **Pegaptanib sodium XXXXXXXX solution for injection**.

Pegaptanib sodium is a selective Vascular Endothelial Growth Factor (VEGF) antagonist. It is a pegylated modified oligonucleotide that binds with high specificity and affinity to extracellular VEGF165, which is the VEGF isoform preferentially involved in pathological ocular neovascularisation. As a consequence, pegaptanib sodium blocks signalling events and the proliferative and vascular permeability responses associated with the binding of VEGF165 to endothelial cells. Pegaptanib sodium does not bind to any significant degree to VEGF121, an isoform which is critical for normal vessel development in the retina and elsewhere under normal physiological conditions.

The proposed indication is for the treatment of all types of exudative age-related macular degeneration (AMD).

- **Posaconazole XXXXXXXX oral suspension**.

Posaconazole is a broad spectrum triazole antifungal that has been developed for the treatment of invasive fungal infections. It is a potent inhibitor of the enzyme lanosterol 14α-demethylase, which catalyses an essential step in ergosterol biosynthesis. Ergosterol depletion, coupled with the accumulation of methylated sterol precursors, is thought to impair membrane integrity and the function of some membrane-associated proteins. This results in the inhibition of cell growth and/or cell death.

Consequently, posaconazole exhibits broad-spectrum antifungal activity against a variety of yeasts and moulds.

The proposed indication is for use in the treatment of the following invasive fungal infections in patients 13 years of age or older:

- Invasive aspergillosis in patients with disease that is refractory to, or are intolerant of, amphotericin B, itraconazole or voriconazole.
- Oesophageal candidiasis or candidemia in patients with disease that is refractory to, or who are intolerant of, amphotericin B, fluconazole or itraconazole.
- Fusariosis, zygomycosis, cryptococcosis, chromoblastomycosis, and mycetoma in patients with disease refractory to other therapy, or patients who are intolerant of other therapy.
- Coccidioidomycosis.

- **Solifenacin succinate XXXXXXXX tablets**.

Solifenacin is a competitive muscarinic receptor antagonist with selectivity for the urinary bladder over salivary glands in vivo. Muscarinic receptors play an important

role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle and stimulation of salivary secretion.

The proposed indication is for the treatment of unstable bladder with symptoms of increased urinary urgency, frequent micturition and/or urge incontinence.

DISCUSSION

The Committee noted that the extract from JAMA's (The Journal of the American Medical Association) review of the safety profile of muraglitazar raised some issues in relation to cardiovascular and cancer risks.

The Committee was advised that the registration application for the drug containing muraglitazar was withdrawn in New Zealand given the safety concerns on the substance. Members deliberated whether the substance should be included in S4 given its safety issues but it was advised that muraglitazar had been approved by the Federal Drug Administration in the US and that individuals wishing to import this substance into Australia personal use could legally obtain up to three months supply each time an import permit was issued. On this basis, the Committee that muraglitazar should be included in S4.

DECISION 2006/46 - 41

The Committee agreed to include fulvestrant, palonosetron, terlipressin, alemtuzumab, anecortave, entecavir, erlotinib, muraglitazar, nesiritide, pegaptanib, posaconazole, and solifenacin in Schedule 4 of the SUSDP to harmonise with New Zealand.

Schedule 4 – New entries

ALEMTUZUMAB.

ANECORTAVE.

ENTECAVIR.

ERLOTINIB.

FULVESTRANT.

MURAGLITAZAR.

NESIRITIDE.

PALONOSETRON.

PEGAPTANIB.

POSACONAZOLE.

SOLIFENACIN.

TERLIPRESSIN.

17.

[Item deleted**]**

18. MATTERS REFERRED BY THE MEDICAL DEVICES EVALUATION COMMITTEE (MDEC)

No item was considered.

19 - 20.

[Items deleted**]**

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES AND ERRATA

21.1.1 NOMENCLATURE FOR CERTAIN CEPHALOSPORIN ANTIBIOTICS (CEPHALORIDINE, CEPHACETRILE, CEPHAMANDOLE, CEPHAPIRIN AND CEPHAZOLIN).

PURPOSE

The Committee considered nomenclature for certain cephalosporin antibiotics (cephacetrile, cephaloridine, cephamandole, cephapirin and cephazolin).

BACKGROUND

At the November 1975 Poisons Scheduling Committee (PSC) Meeting the Committee included cephazolin in Schedule 4. At the November 1988 NDPSC Meeting the Committee agreed to amend the cephazolin Schedule 4 entry to include the current cross-reference to cefazolin.

At the February 1977 PSC Meeting, cephapirin was included in Schedule 4 following consideration of the 71st ADEC Meeting reports.

At the August 1977 PSC Meeting the Committee, following consideration of the 72nd and 73rd ADEC Meeting reports, included cephacetrile in Schedule 4.

At the May 1978 PSC Meeting the Committee considered a list of specific antibiotics based on the NSW Poisons List which could be inserted in Schedule 4 in place of the existing blanket entries. The Committee agreed to this proposal and included several antibiotics, including cephaloridine, in Schedule 4.

At the August 1979 PSC Meeting the Committee, following consideration of the 83rd, 84th and 85th ADEC Meeting reports, included cephamandole in Schedule 4. At the November 1988 NDPSC Meeting the Committee agreed to amend the cephamandole Schedule 4 entry to include the current cross-reference to cefamandole.

At the October 2005 NDPSC Meeting the Committee considered recommendations from the 14th (October 2005) Meeting of the Trans Tasman Harmonisation Working Party (TTHWP) in relation to the harmonisation of a number of substances including cephacetrile, cephaloridine, cephamandole, cephapirin and cephazolin. The substances were considered by the TTHWP as they were identified as unharmonised in the OZNZ Scheduling database on the basis of nomenclature differences.

DISCUSSION

The Committee was reminded of the following points discussed at the October 2005 NDPSC Meeting:

- Cephacetrile, cephaloridine, cephamandole and cephapirin: The Committee noted the entries for the above substances did not include the recommended International Non-proprietary Name (INN), and therefore, agreed that the entries for ‘cefacetrile’, ‘cefaloridine’, ‘cefamandole’ and ‘cefapirin’ should be amended to harmonise with New Zealand.
- Cephazolin: The Committee noted that cephazolin was currently unharmonised due to a duplication of the substance entry in New Zealand (cephazolin and cefazolin). The Members agreed that Australia would amend the S4 entry to cefazolin (INN) and recommend to New Zealand that it delete the duplicate entry (cephazolin). The Committee was advised by the Secretariat that this last recommendation was referred to New Zealand following the October 2005 NDPSC Meeting.

[Paragraph deleted**]**

DECISION 2006/46 - 42

The Committee agreed to minor editorial amendments to the nomenclature for cephaloridine, cephacetrile, cephamandole, cephapirin and cephazolin to harmonise with New Zealand by adoption of the INNs for these substances. The Committee further agreed to maintain the old nomenclature as cross-references in the index for clarity.

Schedule 4 – Amendments

CEPHACETRILE – Amend entry to read:

CEFACETRILE.

CEPHALORIDINE – Amend entry to read:

CEFALORIDINE.

CEPHAMANDOLE – Amend entry to read:

CEFAMANDOLE.

CEPHAPIRIN – Amend entry to read:

CEFAPIRIN.

CEPHAZOLIN – Amend entry to read:

CEFAZOLIN.

21.1.2 NOMENCLATURE OF PIRFENOXONE SODIUM (CATALIN)

PURPOSE

The Committee considered the nomenclature for pirfenoxone sodium (catalin).

BACKGROUND

At the January and June 1969 Poisons Scheduling Committee (PSC) Meetings the Committee considered advice that a product, catalin eye-drops for the treatment of cateracts, was being imported but that the active was not scheduled. The Members agreed to include 1-hydroxy-pyrido(3,2,-a)-5-phenoxazone-3-carboxylic acid (the chemical name of catalin) in Schedule 4.

At the November 1988 Drugs and Poisons Schedule Committee (DPSC) Meeting the Committee noted that 1-hydroxy-pyrido(3,2,-a)-5-phenoxazone-3-carboxylic acid was also known as pirfenoxone or catalin. The Members agreed to amend the Schedule 4 entry to read: CATALIN. At the February 1991 DPSC Meeting the Committee agreed to amend the Schedule 4 catalin entry to the current entry – PIRFENOXONE SODIUM (catalin).

At the October 2005 NDPSC Meeting the Committee considered recommendations from the 14th (October 2005) Meeting of the trans-Tasman Harmonisation Working Party (TTHWP) in relation to the harmonisation of a number of substances including pirfenoxone sodium. The substances were considered by the TTHWP as they were identified as unharmonised in the OZNZ Scheduling database.

DISCUSSION

The Committee were reminded of the following points discussed at the October 2005 NDPSC Meeting:

- The Committee noted that pirfenoxone sodium was currently unharmonised due a nomenclature difference between Australia and New Zealand, i.e. pirfenoxone sodium vs. pirfenoxone (New Zealand). The recommended International Non-propriety Name (INN) for this substance was pirenoxine. New Zealand also had a separate entry in Part I for catalin, which was the common name for pirfenoxone.
- The October 2005 NDPSC Meeting agreed to consider amending the Schedule 4 entry to adopt the INN into the SUSDP at the February 2006 NDPSC Meeting.
- Additionally, the Committee agreed to recommend to New Zealand as an outcome of the February 2006 NDPSC Meeting to consider replacing the entry for pirfenoxone with pirenoxine, and reconsider the need for retaining a separate entry for catalin in Part I. The Committee was advised by the Secretariat that this last recommendation was referred to New Zealand following the October 2005 NDPSC Meeting.

DECISION 2006/46 - 43

The Committee agreed to an editorial amendment to the nomenclature for pirfenoxone sodium (catalin) to harmonise with New Zealand by adoption of the INN for this substance. The Committee further agreed to maintain the old nomenclature as a cross-reference in the index for clarity.

Schedule 4 – Amendment

PIRFENOXONE – Amend entry to read:

PIRENOXINE (catalin).

21.1.3 NICOTINE

PURPOSE

The Committee considered minor editorial rewording of the Schedule 7 entry for nicotine to clarify that the exemption for chewing gum, lozenges, or preparations for sublingual or transdermal use was to only apply when for use as an aid in withdrawal from tobacco smoking.

BACKGROUND

At the October 2003 NDPSC Meeting the Committee agreed to exempt nicotine in gums and transdermal patches from the requirements of scheduling to harmonise the scheduling

outcome with New Zealand. The Committee was of the view that widening the availability of Nicotine Replacement Therapy (NRT) products should encourage more smokers to quit smoking, and as a first step, this approach should improve public health outcomes. This decision was confirmed at the February 2004 NDPSC Meeting following consideration of post-meeting comments. The October 2003 NDPSC Meeting also agreed to foreshadow consideration at the February 2004 meeting of a proposal to exempt nicotine in lozenges for consistency with nicotine in chewing gum and transdermal patches.

At the February 2004 NDPSC Meeting the Committee agreed to exempt nicotine lozenges for NRT on the basis of experience with the availability of such lozenges as a 'Pharmacy Only' medicine and the need to broaden options for smoking cessation.

At the February 2005 NDPSC Meeting the Members agreed to foreshadow consideration of an exemption for nicotine in sublingual tablets at the June 2005 NDPSC Meeting on the grounds of harmonisation with NZ.

At the June 2005 NDPSC Meeting the Committee considered the foreshadowed amendments and agreed, in the interests of harmonisation with New Zealand, to adopt the recommendations as foreshadowed at the February 2005 NDPSC Meeting to exempt sublingual tablets from scheduling. The current nicotine entries therefore exempt chewing gum, lozenges, or preparations for sublingual or transdermal use from scheduling.

DISCUSSION

The Committee considered advice from the XXXXXXXX Member that in wording the June 2005 nicotine decision the Committee had inadvertently introduced a potential loophole. The XXXXXXXX Member noted that:

- Before this decision the old entry placed nicotine products such as chewing tobacco in Schedule 7.
- However, with the new entry (which included exemptions for nicotine in chewing gum, lozenges, for sublingual use, or in preparations for transdermal use) it could be argued that chewing tobacco was "for sublingual use" and so exempt.
- Additionally, this wording opened the possibility that the supply of chewing gum, lozenges etc containing nicotine would be both exempt from scheduling and without regulation as long as no therapeutic benefit was claimed.
- The Member asserted, and the Committee agreed, that such outcomes were not the intent of the Committee in wording its June 2005 decision.

The XXXXXXXX Member recommended that the exemptions from the Schedule 7 nicotine entry be reworded along the lines of:

- Except for use as an aid in withdrawal from tobacco smoking in chewing gum, lozenges, or preparations for sublingual or transdermal use.

The Committee was advised that the XXXXXXXX Member's concerns were circulated to jurisdictional Members prior to the February 2006 NDPSC Meeting for comment. The only comment received was from the XXXXXXXX Member, whose email included:

- A suggestion that it could be easier to just mention the therapeutic use "for use as an aid in withdrawal from tobacco" for the exemption rather than specifying the route of administration. This would leave the decision of whether a formulation was appropriate with the registration authority. The Committee, however, generally agreed that there was value in maintaining the specificity of the entry at this time.
- A note that in WA nasal snuff was currently exempted from Schedule 7.
- The XXXXXXXX Member agreed with the XXXXXXXX Member that there was a need to ensure that chewing tobacco remained in Schedule 7.

The Committee also noted an article from the Medical Journal of Australia (MJA 2005; 183 (6): 334) discussing the availability of smokeless tobacco products in south Asian grocery shops in Sydney. The Members noted that 50 of the 53 shops surveyed sold smokeless tobacco.

DECISION 2006/46 - 44

The Committee agreed to an editorial amendment to the nicotine entries to clarify that, in line with the intent of the June 2005 NDPSC Meeting, the exemption for chewing gum, lozenges, or preparations for sublingual or transdermal use was to only apply when for use as an aid in withdrawal from tobacco smoking.

Schedule 7 - Amendment

NICOTINE – amend entry to read:

NICOTINE **except**:

(a) when included in Schedule 2, 4 or 6;

(b) in tobacco prepared and packed for smoking; or

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