Commonwealth Department of Health and Ageing

TGA THERAPEUTIC GOODS ADMINISTRATION

National Drugs and Poisons Schedule Committee

Record of the Reasons

38th Meeting
17-19 June 2003

Section 52D(2) of the *Therapeutic Goods Act 1989* (the Act) provides the power for the NDPSC to amend the Poisons Standard or prepare a new Standard. The NDPSC takes into account relevant matters mentioned in Section 52E of the Act when making a scheduling decision. The *Record of the Reasons* contains the basis of scheduling decisions and other outcomes arising from the meeting. Please note that the *Record of the Reasons* includes extracts from the NDPSC minutes which have been edited to remove confidential information.

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GLOSSARY

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

CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonisation
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
DAP	Drafting Advisory Panel
DSEB	Drug Safety and Evaluation Branch
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
HCN	Health Communication Network
INN	International Non-proprietary Name
ISO	International Standards Organization
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance
LC_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.

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

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

1.8 NDPSC WORKING PARTIES

1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY (MEDICINES)

1.8.1.1.1 DEFINITION OF TERM "COMPOUNDED"

PURPOSE

The Committee considered recommendations from the TTHWP (M) in relation to the use of the term "compounded" in the SUSDP.

BACKGROUND

The primary use of the term "compounded" is in relation to entries for controlled substances to refer to mixtures with therapeutically active substance(s) that discourage abuse and/or diversion through physical separation of the active components.

Both the SUSDP and the NZ Misuse of Drugs Act definitions for "compounded" are derived from the UN Single Convention on Narcotic Drugs.

These definitions are for Australia (SUSDP):

"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 simple dissolution or other simple physical means.

and for New Zealand as taken from the Misuse of Drugs Act:

Compounded with one or more pharmacologically active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield which would constitute a risk to health.

DISCUSSION

Members noted the different legislative environments in each country with regard to regulation of controlled substances and the differing judicial interpretations incorporated into the different definition of compounded in each country.

Members agreed with the approach to move to harmonised outcomes eg common labelling, where exactly harmonised entries or definitions were not feasible, as in this case.

OUTCOME

On the grounds of the differing legislative environment, the Committee endorsed Decision 8/1 of the working party and:

- acknowledges the differences in definitions for "compounded" between Australia and New Zealand and agrees that the definition for "compounded" remain unharmonised;
- supports a common regulatory outcome for the scheduling of OTC medicines containing controlled substances;
- supports the adoption of common guidelines to achieve common regulatory outcomes for the scheduling of OTC medicines containing controlled substances based on the existing definitions for "compounded";
- directs the working party to prepare draft guidelines within the above terms for consideration by the NDPSC; and
- recommends this approach for consideration by the NZ MOH.

1.8.1.1.2 USE OF TERM "COSMETIC"/ HYDROQUINONE

PURPOSE

The Committee considered recommendations by the TTHWP (M) in relation to the harmonisation of entries containing the term "cosmetic" and the scheduling of hydroquinone.

BACKGROUND

The term "cosmetic use" is used to modify the scope of entries in Schedules 2,4,5 and 6 in the SUSDP. There is no equivalent usage in New Zealand, as cosmetic uses are not controlled under the Medicines Act in New Zealand.

DISCUSSION

The Committee noted the legislative differences between the two countries regarding the control of cosmetics and endorsed Decision 8/2 of the working party in respect of use of this term “cosmetic use”.

The need for a formal definition of “cosmetic use” was questioned and the Committee considered the Trade Practices definition as a possibility. However, members agreed to continue the existing practice of using the dictionary definition as this approach was sufficient for the Jurisdictions.

Members recalled that the scheduling of hydroquinone had originally revolved around the severe skin irritation noted above concentrations of 2% and the potential to mask melanomas through the bleaching effect on the skin. In addition, members accepted that

additional controls were justified on any preparation that may increase the incidence of solar induced skin cancers given the current public health concerns over the epidemic of skin cancer in each country.

The Committee was advised by XXXXXXXXX of TTHWP(M) that a further recommendation in relation to a Part III entry for hydroquinone would be included in the minutes of the 9th meeting of the working party.

Members agreed that all the recommendations in respect of hydroquinone be considered together at the October 2003 meeting.

OUTCOME

On the grounds of differing legislative environment, the NDPSC agreed that where the term "cosmetic use" is used, the wording for the entry will remain unharmonised with New Zealand.

The Committee agreed to defer referral of the recommendation below to allow consideration in conjunction with the recommendation on hydroquinone arising from the 9th meeting of the TTHWP (M).

On the grounds of harmonisation with New Zealand the NDPSC recommends that the NZ MOH consider adoption of a similar Part I entry for hydroquinone for human therapeutic use. That is move the existing Part III entry to Part I:

HYDROQUINONE; in medicines containing more than 2%.

1.8.1.1.3 ASPIRIN, PARACETAMOL AND SALICYLAMIDE - SCHEDULE 4 ENTRY

PURPOSE

The Committee considered recommendations by the TTHWP (M) for the harmonisation of the Schedule 4 entries for aspirin, paracetamol, and salicylamide. This Item should be read in conjunction with Item 1.8.1.1.4 Aspirin and Item 1.8.1.1.5 Paracetamol.

BACKGROUND

Aspirin, paracetamol and salicylamide were included in Schedule 4 when in combination with each other or with caffeine, in recognition of the association of such combinations with severe nephrotoxicity. New Zealand has no equivalent entry in Part I for these substances.

DISCUSSION

Members recalled that the decision to include multi-analgesic and analgesic combinations with caffeine in Schedule 4 had been specifically taken to address a public health

problem in Australia (analgesic nephropathy) associated with the use of these products. The decision had been based on reports in the medical literature, along with recommendations from the NH&MRC, the Analgesics Working Party, and the Medicines Advisory Committee. The issue had also been extensively discussed and the decision endorsed in the Senate Standing Committee on Social Welfare report *Drug Problems in Society - An intoxicated Society (1977)*.

Members were advised that the additional restrictions included in the recommendation on paracetamol had been added to cover subsequent amendments to the SUSDP in relation to inclusion of modified-release preparations of paracetamol in Schedule 2. Members noted that while it was unlikely that New Zealand would adopt a similar upper limit (650mg) for divided dose preparations, as all such preparations containing more than 500mg of paracetamol remained prescription medicines in New Zealand, New Zealand was still likely to adopt the entry in principle.

Members agreed to endorse decision 8/3 of the working party holding over the recommendations in relation to paracetamol and aspirin for action following consideration at the October 2003 meeting of the foreshadowed amendments for paracetamol and aspirin from Items 1.8.1.1.4 and 5.

OUTCOME

THE COMMITTEE ENDORSED DECISION 8/3 OF THE WORKING PARTY AND RECOMMENDED TO THE NZ MOH THAT IT INCORPORATE THE FOLLOWING INTO ITS PART I ENTRIES:

- **(FORESHADOWED) ASPIRIN; WHEN COMBINED WITH CAFFEINE, PARACETAMOL OR SALICYLAMIDE OR ANY DERIVATIVE OF THESE SUBSTANCES;**
- **(FORESHADOWED) PARACETAMOL; WHEN COMBINED WITH ASPIRIN, CAFFEINE OR SALICYLAMIDE OR ANY DERIVATIVE OF THESE SUBSTANCES; IN TABLETS OR CAPSULES CONTAINING MORE THAN 650 MILLIGRAMS OF PARACETAMOL; IN INDIVIDUALLY WRAPPED POWDERS OR SACHETS OF GRANULES EACH CONTAINING MORE THAN 1000 MILLIGRAMS OF PARACETAMOL.**
- **SALICYLAMIDE; WHEN COMBINED WITH ASPIRIN, CAFFEINE OR PARACETAMOL OR ANY DERIVATIVE OF THESE SUBSTANCES.**

1.8.1.1.4 ASPIRIN - OTC

PURPOSE

The Committee considered recommendations by the TTHWP (M) in respect of harmonisation of the Schedule 2 entry for aspirin. This item should be read in conjunction with Item 17.1 Warning Statements (Aspirin) and Item 1.8.1.1.3 - Aspirin S4.

BACKGROUND

The primary entry for aspirin is in Schedule 2 for Australia and Schedule 3 (Part II) for New Zealand with exemptions to general sales in both countries. The existing common entries also do not align in respect of cut-offs, pack sizes or inclusion of warning statements.

DISCUSSION

Members noted that despite the equivalent to Schedule 3 as the primary entry, New Zealand has the least restrictive scheduling for the bulk of products as there are no restrictions on strength or quantity for general sales of standard release products.

Members were advised that the working party has taken a stepwise approach leading to harmonisation after hand-over of Appendix F warning statements and safety directions to the TGA in 2004. In addition, the working party agreed on the more restrictive scheduling for quantities and doses more appropriate to the treatment of chronic conditions on public health grounds. These grounds were that such conditions need professional help available when required. This is in line with the NCCTG guidelines for harmonisation. Members noted that the proposal may have a significant impact in New Zealand on tablets or capsules containing more than 325 mg in packs of more than 25 and tablets or capsules containing 325-500mg in packs greater than 16 unit doses. The WP had noted that there were some 35 such products containing 300-325mg aspirin in packs of 40-150 unit doses that would be affected by this proposal.

Members agreed that there appeared to be no public health reason preventing the harmonisation of preparations for the prevention of cardiovascular disease or inhibition of platelet aggregation and foreshadowed an amendment accordingly. It was agreed to hold recommendation (C) over to the October meeting so that all initial recommendations in relation to aspirin would be forwarded as a group to the NZMOH for consideration by MCC.

Members noted that the Scheduling amendments foreshadowed for 2004 provided a way forward to complete harmonisation of regulatory outcomes for aspirin following hand over of Appendix F safety directions and warning statements for therapeutic goods to the TGA in 2004.

OUTCOME

THE COMMITTEE ENDORSED DECISION 8/4 OF THE WORKING PARTY AND AGREED:

A. THAT ON THE GROUNDS OF ACHIEVING HARMONISATION FOR LOW-DOSE ASPIRIN FOR PREVENTION OF CARDIOVASCULAR DISEASE OR INHIBITION OF PLATELET AGGREGATION, FORESHADOW AMENDMENT OF THE SCHEDULE 2 ENTRY FOR ASPIRIN TO READ:

Schedule 2 - amendment (Foreshadowed)

ASPIRIN - amend entry to read:

ASPIRIN **except:**

(a) when included in Schedule 4 or 6;

(b) in individually wrapped powders or sachets of granules each containing 650 mg or less of aspirin as the only therapeutically active constituent other than an effervescent agent when enclosed in a primary pack that:

(i) contains 12 or less such powders or sachets of granules;

(ii) is labelled with the warning statement:

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; and

(iii) includes in the directions for use, in capital letters not less than 1.5 mm in height, the warning statements:

CONSULT A DOCTOR BEFORE GIVING THIS MEDICATION TO CHILDREN OR TEENAGERS WITH CHICKEN POX, INFLUENZA OR FEVER; and

CAUTION - DO NOT GIVE TO CHILDREN UNDER TWO YEARS OF AGE EXCEPT ON DOCTOR'S ADVICE;

(c) in tablets or capsules each containing no other therapeutically active constituent **except** an effervescent agent when:

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

(ii) in a primary pack containing 25 or less tablets or capsules, each containing 325 mg or less of aspirin, or in a primary pack containing 16 or less tablets or capsules, each containing 500 mg or less of aspirin;

(iii) the primary pack is labelled with the warning statement:

WARNING - This medication may be dangerous when used in large amounts or for a long period; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; and

(iv) the directions for use include, in capital letters not less than 1.5 mm in height, the warning statements:

CONSULT A DOCTOR BEFORE GIVING THIS MEDICATION TO CHILDREN OR TEENAGERS WITH CHICKEN POX, INFLUENZA OR FEVER; and

CAUTION - DO NOT GIVE TO CHILDREN UNDER TWO YEARS OF AGE EXCEPT ON DOCTOR'S ADVICE; or

(d) in tablets or capsules each containing no other therapeutically active constituent **except** an effervescent agent when:

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

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

(iii) the primary pack is labelled with the warning statement:

For use under medical supervision only.

B. THAT AT THE OCTOBER 2004 MEETING OF NDPSC, FOLLOWING TRANSFER OF WARNING STATEMENTS TO THE TGA "*Required Advisory Statements for Therapeutic Goods*", FORESHADOWS AMENDMENT OF ITS SCHEDULE 2 ENTRY FOR ASPIRIN TO READ:

Schedule 2 - amendment (Foreshadowed for October 2004)

ASPIRIN - amend entry to read:

ASPIRIN **except**:

(a) when included in Schedule 4 or 6;

(b) in individually wrapped powders or sachets of granules each containing 650 mg or less of aspirin as the only therapeutically active constituent other than an effervescent agent when enclosed in a primary pack containing 12 or less such powders or sachets of granules; or

(c) in tablets or capsules each containing no other therapeutically active constituent except an effervescent agent when in a primary pack containing:

(i) 25 or less tablets or capsules, each containing 325 mg or less of aspirin;

(ii) 16 or less tablets or capsules, each containing 500 mg or less of aspirin; or

(iii) 100 or less tablets or capsules when packed and labelled for the treatment of cardiovascular disease or to inhibit platelet aggregation, each containing 100 mg or less of aspirin.

C. TO RECOMMEND TO THE NEW ZEALAND MINISTRY OF HEALTH THAT IT:

(a) DELETE ITS PART II ENTRY FOR ASPIRIN AND ADOPT THE REVISED SCHEDULE 2 ENTRY (B.) ABOVE INTO PART III; AND

(b) LIAISE WITH THE TGA TO ACHIEVE A HARMONISED POSITION ON THE PACKAGING AND LABELLING OF THE EXEMPT PRODUCTS CONTAINING ASPIRIN, FOR ADOPTION INTO THE NEW ZEALAND REGULATORY GUIDELINES.

1.8.1.1.5 PARACETAMOL

PURPOSE

The Committee considered recommendations by the TTHWP (M) in respect of harmonisation of the Schedule 2 and 3 entries for paracetamol. This item should be read in conjunction with Item 17.1 Warning Statements (Paracetamol) and Item 1.8.1.1.3.

BACKGROUND

Previously, agreement has been reached on pack sizes in S2/Part III at 25 units (500 mg or less) or 12.5 g paracetamol. The XXXXXXXXX had requested the WP consider a restriction to 16 units for general sales but this had been deferred to allow consideration of the Newgreen report.

The existing Scheduling is aligned in respect of there being entries for general sales, Schedule 2 and Schedule 4, The entries are unharmonised with respect to pack and unit dose limits, safety directions and warning statements.

DISCUSSION

Members noted that the working party had proposed a stepwise approach leading to harmonisation after hand over of Appendix F warning statements and safety directions for therapeutic goods to the TGA in 2004. The proposal would result in harmonisation with the less restrictive scheduling position for OTC products. However introduction of more restrictive scheduling for larger quantities and higher dose products reflected the public health concerns with overdose of paracetamol and the potential for use in self-harm.

The New Zealand Representative advised that Australia and New Zealand were potentially harmonised in that the MCC had agreed to the 25 unit-dose (12.5 g) packs and the corresponding dose regimes, where appropriate. The principle points for negotiation now remained the warning statements for paracetamol. At least one of these issues had been resolved in part with the proposal by MEC to include a warning statement in relation to the potential for liver damage. However, the warning statements needed to be finalised before proposals for harmonisation could be completed. The member also advised that the upper limit of 650 mg for OTC tablets and capsules was also unlikely to be harmonised. It was suggested that all of the proposals could be considered as a single package following resolution of the warning statements at the October meeting.

Members agreed to defer further consideration pending resolution of the warning statements at the October meeting.

OUTCOME

THE COMMITTEE ENDORSES DECISION 8/5 OF THE WORKING PARTY AND AGREES:

(A) THAT, ON THE GROUNDS OF PARTIAL HARMONISATION, THE FOLLOWING WORDING FOR THE S4 ENTRY FOR PARACETAMOL IS FORESHADOWED FOR CONSIDERATION AT THE OCTOBER MEETING AND THE NDPSC RECOMMENDS THAT THE NZ MOH ADOPT A SIMLAR REGULATORY OUTCOME IN PART I:

Schedule 4 - amendment (Foreshadowed)

PARACETAMOL:

(a) when combined with aspirin, caffeine or salicylamide or any derivative of these substances;

(b) in tablets or capsules containing more than 650 mg of paracetamol; or

(c) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol.

(B) THAT AT THE OCTOBER 2004 MEETING OF NDPSC FOLLOWING TRANSFER OF WARNING STATEMENTS TO THE TGA "*Required Advisory Statements for Therapeutic Goods*", THE NDPSC CONSIDER AMENDMENT OF THE SCHEDULE 2 ENTRY FOR PARACETAMOL TO READ AS FOLLOWS AND RECOMMENDS THAT THE NZ MOH RECONSIDER ADOPTING A SIMILAR REGULATORY OUTCOME:

Schedule 2 - amendment (Foreshadowed for October 2004)

PARACETAMOL for therapeutic use:

(a) in liquid oral preparations;

(b) in suppositories; or

(c) as the only therapeutically active constituent other than effervescent agents:

(i) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol **except** when in a primary pack containing 12 or less such powders or sachets; or

(ii) in tablets or capsules each containing 650 mg or less of paracetamol **except** when in a primary pack containing 25 or less such tablets or capsules,

and not labelled for the treatment of children 6 years of age or less.

1.8.1.1.6 PYRIDOXINE, PYRIDOXAL, PYRIDOXAMINE

This item was considered under Item 16.2

1.8.1.1.7 CONTROL OF INJECTABLES

PURPOSE

The Committee considered recommendations by the TTHWP (M) in relation to the harmonisation of scheduling for injectable substances.

BACKGROUND

New Zealand has a class entry for injectables in Part III. There is no equivalent to this entry in the SUSDP.

DISCUSSION

The meeting was advised that the working party had amended the wording of the recommendation to read:

THAT THE NDPSC BE ADVISED THAT THE FOLLOWING POLICY QUESTIONS NEED TO BE ADDRESSED:

- IS THERE EVIDENCE OF ABUSE, MISUSE OR CRIMINAL USE OF UNSCHEDULED INJECTABLES INCLUDING VITAMINS, MULTIVITAMINS, POTASSIUM CHLORIDE OR OTHER SALTS, DEXTROSE OR OTHER SUGARS, AND HOMOEOPATHIC INJECTIONS IN AUTRALIA;
- IS THERE A NEED FOR REGULATORY CONTROL OVER THE AVAILABILITY, USE AND ADMINISTRATION OF THESE PRODUCTS TO THE GENERAL PUBLIC; AND
- IF REGULATORY CONTROLS ARE RECOMMENDED, WHAT FORM SHOULD THESE CONTROLS TAKE?

The XXXXXXXX advised that an extensive literature review on control of injectables had highlighted a problem with sterility and administration practices in third world countries but had provided no evidence of any problem in developed countries, in particular Australia and New Zealand.

There was some discussion of the administration of injectable vitamins by complementary medicine practitioners. However, while some jurisdictions were aware of the practice occurring, there was no evidence presented that there may be public health problems arising from this practice. It was noted by the Committee that were this a problem, then control of the act of injecting would require the injection to be placed in Schedule 4 rather than Schedule 2. There was general agreement that this may be considered a rather drastic solution to what was an issue of practitioner control and education.

There was general agreement among members that even if there was currently no evidence of abuse of injectables, this would not limit the ability of any jurisdiction to present such evidence to the Committee in the future.

OUTCOME

The Committee agreed that there was no evidence of the abuse of unscheduled injectables at this time. Accordingly there was no need for regulatory control of these substances through scheduling. If evidence did arise, it would be considered on a case-by-case basis.

1.8.1.1.8 ANTIHISTAMINES

PURPOSE

The Committee considered recommendations of the TTHWP (M) in relation to harmonisation of the scheduling entries for various antihistamines.

BACKGROUND

The general approach to scheduling of the antihistamines is quite different in each country. In Australia the primary entry is in Schedule 4 with single active oral preparations in Schedule 3 with compounded preparations, single active non-sedating antihistamines and preparations for travel sickness in Schedule 2. By contrast, in New Zealand the primary entry was in Part III, preparations for sedation or treatment of anxiety were in Part II and some preparations for travel sickness were general sales.

DISCUSSION

Members were advised that New Zealand had commissioned and recently completed an extensive literature review of the antihistamines of the risks and benefits of the sedating antihistamines. This had identified a number of risks that warranted differentiation of the sedating antihistamines from the non-sedating antihistamines and hence justified a difference in scheduling to alert consumers to these risks.

There was general agreement to the broad principles adopted by the working party to recommend changes for harmonisation, that is:

- Antihistamines and preparations with the potential for serious abuse be included in Schedule 4.

- Single active preparations of sedating antihistamines be included in Schedule 3; and

- Single active preparations of non-sedating antihistamines and specified combination preparations of antihistamines be included in Schedule 2.

Members noted that consideration of the harmonisation of the entries for promethazine, dimenhydrinate, meclozine, diphenhydramine and doxylamine had been completed at the June 2003 meeting of the working party.

Members endorsed decision 8/8 of the working party and agreed that harmonisation should occur on the more restrictive scheduling based on public health concerns with the sedating antihistamines. It was noted that the remaining antihistamines were to be reviewed at the 9th TTHWP (M).

OUTCOME

THE NDPSC RECOMMENDS THAT THE NZ MOH ADOPT THE FOLLOWING CHANGES:

- **ADDITION OF THE FOLLOWING ENTRIES TO PART I**

ANTAZOLINE except in eye drops
AZATADINE except in oral preparations
AZELASTINE except in nasal preparations
BAMIPINE.
BROMPHENIRAMINE except in oral preparations
BUCLIZINE except in oral preparations
CETIRIZINE except in oral preparations
CHLORCYCLIZINE.
CHLORPHENIRAMINE except in oral preparations
CLEMASTINE except in oral preparations
CLEMIZOLE.
CYPROHEPTADINE except in oral preparations.
DESLORATADINE except in oral preparations.
DEXCHLORPHENIRAMINE except in oral preparations
DIMETHINDENE except in oral preparations
DPHENHYDRAMINE except in oral preparations
DIPHENYLPYRALINE except in oral preparations
DOXYLAMINE except in oral preparations
LEVOCABASTINE except in topical eye or nasal preparations
LORATADINE except in oral preparations.
MEBHYDROLIN.
MEPYRAMINE except in oral preparations
METHDILAZINE except in oral preparations

PHENIRAMINE except in oral preparations or eye drops
PHENYLTOLOXAMINE except in oral preparations
PROMETHAZINE?? except in oral preparations
THENYLDIAMINETRIMEPRAZINE except in oral preparation
TRIMEPRAZINE
TRIPROLIDINE except in oral preparations

- **ADDITION OF THE FOLLOWING ENTRIES TO PART II WITH INCORPORATION OF THE ACCOMPANYING NOTES INTO THE REGULATORY GUIDELINES:**

AZATADINE in oral preparations
BROMPHENIRAMINE in oral preparations
BUCLIZINE in oral preparations.
CHLORPHENIRAMINE in oral preparations
CLEMASTINE in oral preparations
CYPROHEPTADINE in oral preparations
DEXCHLORPHENIRAMINE in oral preparations
DIMETHINDENE in oral preparations
DIPHENYLPYRALINE in oral preparations
DOXYLAMINE in oral preparations
MEPYRAMINE in oral preparations
METHDILAZINE in oral preparations
PHENIRAMINE in oral preparations
PHENYLTOLOXAMINE in oral preparations
THENYLDIAMINE in oral preparations
TRIMEPRAZINE in oral preparations in a pack approved by the Minister for Health.
Notes: In solid preparations or in liquid preparations containing 10mg or less of trimeprazine per 5ml.
TRIPROLIDINE in oral preparations.

- **AMENDING THE ENTRIES IN PART III TO READ AS SHOWN WITH INCORPORATION OF THE ACCOMPANYING NOTES INTO THE REGULATORY GUIDELINES:**

AZELASTINE in preparations for nasal use.
CETIRIZINE in oral preparations.
BROMPHENIRAMINE in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.
CHLORPHENIRAMINE in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.

DESLORATIDINE in preparations for oral use.
DEXCHLORPHENIRAMINE in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.
DIPHENYLPYRALINE in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.
LEVOCABASTINE in topical eye or nasal preparations
LORATIDINE in preparations for oral use.
PHENIRAMINE in eye drops or in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.
THENYLDIAMINE in nasal preparations for topical use or in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.
TRIMEPRAZINE in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.
TRIPROLIDINE in a pack approved by the Minister for Health.
Notes: when combined with one or more of the following substances, an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine, or pseudoephedrine and labelled for the treatment of adults or children above the age of two.

- **DELETING THE FOLLOWING ENTRIES FROM PART III:**

CHLORCYCLIZINE.
CLEMIZOLE.
MEBHYDROLIN.

1.8.1.1.9 VITAMIN A

PURPOSE

The Committee considered the status of harmonisation in relation to the entries for Vitamin A.

BACKGROUND

The NDPSC last considered the scheduling of Vitamin A at the November 2000 meeting where the required warning statements were finalised for exempt products. The New Zealand MCC has declined to harmonise at this level and has established a less restrictive entry.

DISCUSSION

Members recalled that the advice from MCC had been gazetted and discussed at the November 2000 meeting of NDPSC. However no decision had been documented at the time that the entry was unable to be harmonised and it be placed on the two-year list for reconsideration.

Members agreed that any decision to include Vitamin A on the list of unharmonised substances would date from present meeting.

OUTCOME

The Committee agreed that the entry for Vitamin A remain unharmonised on the grounds of differing dietary intake of Vitamin A in the two countries, and be placed on the list of unharmonised substances for reconsideration on or before two years from the current meeting (June 2005)

1.8.1.1.10 ZINC COMPOUNDS

PURPOSE

The Committee considered recommendations from the TTHWP (M) in relation to the harmonisation of scheduling for zinc compounds.

BACKGROUND

The entries for zinc chloride have been previously harmonised and an equivalent regulatory outcome has been achieved for zinc pyrithione. The Australian entry for the remaining internal therapeutic uses of zinc compounds include a Schedule 4 entry above a daily dose of 50mg with warning statements required between daily doses of 25 and 50mg/day. The New Zealand zinc entry for internal use, is included in Part I for a daily dose above 25mg/day.

DISCUSSION

There was considerable discussion of the proposed changes to the warning statements included in the Schedule 4 entry. In particular it was pointed out that both of the terms "for a long period" and "for a long time" appeared equally vague. Members recalled that the change from "for a long period" to "for a long time" had originated with products for treatment of pre-menstrual conditions such as pyridoxine where there was some

likelihood of confusion with the "menstrual period" rather than a "time interval". Accordingly the word time had become generally preferred over period.

Members noted that following hand over of the Appendix F warning statements for therapeutic goods to the TGA in 2004, these would no longer be the responsibility of the NDPSC. Further, it was noted that the "Performance Based Labelling" project was designed to address such issues as raised above. Some members questioned why a recommendation in relation to reviewing the warning statements was required at all as the issue for this committee was achieving harmonisation of scheduling.

XXXXXXXXX advised the Committee that removal of the warning statements for exempt products from the schedule entry would facilitate harmonisation as the issue of the warning statements could then be addressed through regulatory avenues other than the Medicines Act in New Zealand. Members agreed that recommendation (B) from TTHWP (M)8 in relation to reviewing the warning statements be struck from the proposal.

Members noted that endorsement of the recommendation (C) of the working party would result in harmonisation in 2004 at the least restrictive schedule.

OUTCOME

THE COMMITTEE ENDORSES DECISION 8/10 OF THE WORKING PARTY AND:

(A) RECOMMENDS THAT NZ MOH ADOPT A SIMILAR REGULATORY OUTCOME TO THE EXISTING SCHEDULE 4 ENTRY FOR ZINC, THAT IS ADOPTION OF A 50MG/DAY (ZINC) CUT-OFF FOR GENERAL SALES AND INCORPORATION OF THE WARNING STATEMENTS INTO THE RELEVANT GUIDELINES.

(B) AT THE OCTOBER 2004 MEETING OF NDPSC FOLLOWING TRANSFER OF WARNING STATEMENTS TO THE TGA "*Required Advisory Statements for Therapeutic Goods*", THE NDPSC FORESHADOWS AMENDMENT OF THE SCHEDULE 4 ENTRY FOR ZINC COMPOUNDS TO READ:

Schedule 4 - amendment (Foreshadowed for October 2004)

ZINC COMPOUNDS - amend entry to read:

ZINC COMPOUNDS for human internal use **except** in preparations with a recommended daily dose of 50mg or less.

1.8.1.1.11 AMPHOTERICIN

PURPOSE

The Committee considered recommendations by the TTHWP (M) in relation to the harmonisation of the scheduling of amphotericin.

BACKGROUND

Discussion of a number of human antibiotics and antifungals had been deferred by the working party pending finalisation and consideration of the Australian Government response to JETACAR. The Commonwealth response and implementation has been finalised through the Commonwealth Inter-agency Joint Implementation Group.

DISCUSSION

Members recalled that antifungals were outside the scope of the Australian Government response to the JETACAR.

Members noted that nystatin and miconazole are available in Schedule 3 for the treatment of oral candidiasis and that New Zealand has a Part II entry for amphotericin but this is restricted to Schedule 4 in Australia

Members noted that inclusion of amphotericin in Schedule 3 would be consistent with nystatin and miconazole for a similar use and that this would align harmonisation with the least restrictive scheduling for this use. As this had not been gazetted, members agreed that the recommendation be foreshadowed for consideration at the next meeting.

OUTCOME

THE COMMITTEE ENDORSES DECISION 8/11 OF THE WORKING PARTY AND AGREES THAT ON THE GROUNDS OF HARMONISATION WITH NEW ZEALAND, AMPHOTERICIN BE INCLUDED IN SCHEDULE 3 FOR ORAL CANDIDIASIS.

Schedule 3 - New entry (Foreshadowed)

AMPHOTERICIN for human use in topical preparations for the treatment of oral candidiasis.

Schedule 4 - amendment (Foreshadowed)

AMPHOTERICIN - amend entry to read:

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

1.8.1.1.12 NZ MISUSE OF DRUGS ACT AND HARMONISATION OF CONTROLLED SUBSTANCES LABELLING.

PURPOSE

The Committee considered recommendations by the TTHWP (M) for the harmonisation of labelling requirements for Schedule 8 substances and controlled substances in other Schedules with the NZ Misuse of Drugs Act.

BACKGROUND

Control over the labelling and availability of controlled substances in New Zealand is through the NZ Misuse of Drugs Act rather than through the medicine schedules as in Australia. Controlled substances represent the largest remaining group of unharmonised medicines between Australia and New Zealand.

This issue was last considered by the Committee at the June 2002 meeting where the harmonisation of NZ labelling requirements under the Misuse of Drugs Act for Schedule 8 substances was discussed but not resolved.

DISCUSSION

Members were advised that the labelling issue for harmonised controlled drugs had been discussed further at the June 2003 meeting of the working party. At this meeting members of the working party had agreed that the approach proposed at the October 2002 meeting may provide a way forward on the harmonisation of scheduling for controlled substances in Schedules 2,3, and 4. This would be to harmonise the labelling in other Schedules of the SUSDP recognising that the differing legislative environments made harmonisation of the schedule entries unlikely in the near term..

There was general support for investigating options for labelling schemes that met both Australian and New Zealand labelling requirements. However, it was agreed that practically, this would require preparation of label mock-ups for consideration by both the NDPSC and MCC.

XXXXXXXXX agreed to assist the Secretariat in preparing example labels for consideration by the working party.

Members agreed that given on-going proposal to achieve at least partial harmonisation, the third and fourth dot-points of decision 8/12 from the working party be struck out.

OUTCOME

THE COMMITTEE ENDORSED THE AMENDED DECISION 8/12 OF THE WORKING PARTY AND AGREED THAT ON THE GROUNDS OF PARTIAL HARMONISATION, TO:

- **FORESHADOW AMENDMENT OF PART 2, PARAGRAPH 7(1)(a)(iv) TO READ:**

Part 2, LABELS AND CONTAINERS - amendment (Foreshadowed)

Amend sub-paragraph 7(1)(a)(iv) to read:

(iv) if the poison:

(A) is a Schedule 5 poison, with nothing, other than a Class label as specified in the *Australian Code for the Transport of Dangerous Goods by Road and Rail* or a statement of the principal hazard of the poison, written on that line;

(B) is a Schedule 8 poison, with nothing, other than a NZ designation as specified in the New Zealand *Misuse of Drugs Act* (1975) preceded by the letters NZ, written on that line ;

(C) is not a Schedule 5 or a Schedule 8 poison , with nothing, other than a Class label as specified in the *Australian Code for the Transport of Dangerous Goods by Road and Rail*, written on that line;

- **RECOMMEND TO THE NZ MOH THAT THEY VARY THE LABELLING REQUIREMENT FOR CONTROLLED DRUGS INCLUDED IN SCHEDULE 8 OF THE SUSDP TO INCLUDE THE LETTERS "NZ" PRECEDING THE DESIGNATION FOR THE CONTROLLED SUBSTANCE.**

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

There were no items for consideration.

2.2 SUSDP, PART 2

2.2.1 LABELLING OF HAIR DYE PRODUCTS

PURPOSE

The Committee considered a proposal seeking to amend the labelling requirements for containers of single application hair dyes included in Schedule 5.

BACKGROUND

The existing requirement for containers under Part 1, paragraph 23(1) for Schedule 5 poisons was as follows:

"**23.** (1) The container in which any Schedule 5 poison is sold or supplied must:

(a) comply with the container requirements of paragraph 21 or paragraph 22; or

(b) be readily distinguishable from a container in which food, wine or other beverage is sold; and

(i) comply with sub-section 1.4 (General Requirements) of Australian Standard AS 2216 – 1997 excluding paragraph 1.4.3;

(ii) be securely closed and, except when containing a preparation for use on one occasion only, be capable of being re-closed to prevent spillage of its contents; and

(iii) have the expression "POISON", "NOT TO BE TAKEN" or "NOT TO BE USED AS A FOOD CONTAINER" embossed or indelibly written thereon or, in the case of a fibreboard container, written on a paper label which cannot be removed without damage to the container."

DISCUSSION

XXXXXXXXX sought approval to allow the use of a label affixed to bottles of Schedule 5 single application hair dyes, using a permanent adhesive as an alternative to embossing or indelibly writing the abovementioned expression on such bottles. The Committee noted the following points raised in support of its proposal:

- XXXXXXXXX was unable to comply with existing labelling requirements in the SUSDP for Schedule 5 containers. Consequently, companies for the past few years had been applying individually to obtain exemptions from each State or Territory. Such exemptions had been granted on an annual basis to allow S5 hair dyes with a permanently adhered label containing the words "Not to be taken" or "Poison" to be marketed, instead of the same words being embossed or indelibly written on the immediate container. This approach to managing the problem was not only clumsy and time consuming, but also resulted in disputes over the definition of "permanently adhered label".

- There were definitions for "permanently adhered label" in use within the Packaging industry and pharmaceutical industry. XXXXXXXXX proposed that the following definition be adopted to resolve the confusion:

  " Permanent Adhesive Label - an adhesive designed to adhere to a substrate without the edge lifting which cannot be removed without damaging either the label or the substrate."

- The use of non-embossed labels, affixed by means of a permanent adhesive, was a viable and globally acceptable alternative, which was compatible with the requirements of AS2216-1997 (Packaging for Poisonous Substances). AS2216-1997 recognised the use of permanently adhered labels as shown in the following:

  Section 4 for Flexible Containers at 4.5 – Tactile Identification stated "Where the immediate container cannot be readily separated from the primary pack, the poison symbol shall be placed on the primary pack in accordance with Clause 1.5. The poison symbol may be applied as an embossed label affixed by means of a permanent adhesive."

  "Where the immediate container is a single use sachet, the poison symbol shall be placed either on the primary pack or on the immediate container."

  Section 6 for Fibreboard and Paperboard Containers including Composite Cans at 6.5 – Tactile Identification, stated "The poison symbol may be applied as an embossed label affixed by means of a permanent adhesive."

- Internationally, there were no requirements to use embossed or indelibly written statements on containers of Schedule 5 hair dyes as existed in Australia. In Europe, the USA and Canada, permanently fixed labels were permitted to be used, provided there were no other packaging requirements.

The Committee noted the submission from XXXXXXXXX which raised the following points:

- Over the last few years, XXXXXXXXX had been assisting Victorian companies comply with the requirements specified under Part 2, paragraph 23(1)(b)(iii), following the detection of many cases of non-compliance involving car care products, cleaning chemicals, hair care preparations and agvet chemicals.
- Some smaller manufacturers indicated that they were unable to find a source for containers, which comply with existing Australian requirements. Additionally, an increasing number of manufacturers had advised XXXXXXXXX that their products were manufactured overseas and that while their labels were printed to Australian requirements, they were unable to comply with container requirements due to the low proportion of the finished products being supplied to the Australian market.
- Whilst the XXXXXXXXX application covered only hair dye products in Schedule 5, the available information suggested that a much wider range of products were affected. Given the current climate of global harmonisation, the problem was

anticipated to increase. On this basis, XXXXXXXXX supported the XXXXXXXXX proposal and proposed to include all Schedule 5 containers in the proposed amendment.

OUTCOME

The Committee recognised the constraints affecting the ability of various industry sectors to comply with the labelling requirements specified under Part 2, paragraph 23(1)(b)(iii) of the SUSDP and agreed to extend the proposed amendment to include all containers for Schedule 5 poisons. The Committee was of the view that this approach provided a mechanism for harmonisation of labelling of Schedule 5 containers across all jurisdictions, which would be compatible with AS2216-1997 (Packaging for Poisonous Substances) and internationally accepted labelling practices. Furthermore, the Committee also supported the inclusion of a definition for a "permanent adhesive label" in the proposed amendment to avoid the potential for confusion.

The Committee agreed to foreshadow this decision, which was to be finalised at the October 2003 meeting to facilitate appropriate public consultation.

FORESHADOW

Part 2, paragraph 23(1) – Amendment

Part 2, paragraph 23(1)(b)(iii) – amend entry to read:

23. (1) The container in which any Schedule 5 poison is sold or supplied must:

(iii) have the expression “POISON”, “NOT TO BE TAKEN” or “NOT TO BE USED AS A FOOD CONTAINER” embossed or indelibly written thereon, or printed on a permanent adhesive label designed to adhere to a substrate without lifting and which cannot be removed without damaging either the label or the substrate.

2.3 SUSDP, PART 3

2.3.1 PACKAGING OF SCHEDULE 8 PRODUCTS

PURPOSE

The Committee considered the proposal to include new container requirements for Schedule 8 poisons under Part 3 of the SUSDP.

BACKGROUND

Existing provisions specified in Part 3 in the SUSDP covering sale or supply did not include Schedule 8 poisons.

DISCUSSION

The Committee was advised that the NSW Poisons legislation contained packaging provisions to ensure that containers of Schedule 8 drugs (drugs of addiction) for sale or supply were sealed in such a way that it was easy to distinguish broken seals. XXXXXXXXX proposed that similar provisions be included in the SUSDP, on the grounds that Part 3 of the SUSDP made recommendations to the jurisdictions for incorporation into their legislation.

Members were informed that most companies routinely packaged drugs of addiction with tamper evident sealing for safety reasons. However, recently it came to the attention of XXXXXXXXX that some primary packs were not so sealed, with manufacturers relying on the fact that the (immediate) container was presented in a blister pack.

The Committee understood the intent of the requirement is to provide some degree of assurance to persons in the supply chain that they have received the package intact for supply/dispensing to their clients.

OUTCOME

The Committee supported the proposal on the following grounds:

- consumer safety;
- reduce the potential for diversion to illicit use or abuse; and
- the inclusion of provisions for packaging Schedule 8 products for sale or supply in Part 3 of the SUSDP would provide a vehicle for harmonisation across all jurisdictions.

The Committee also agreed to foreshadow consideration of the proposed amendment at the October 2003 meeting to facilitate appropriate public consultation.

FORESHADOW

Part 2 – New entry

Schedule 8 poisons

41A. A person who supplies any Schedule 8 posion must ensure that the Schedule 8 poison is packaged in such a way that its primary pack is so sealed that, when the seal is broken, it is readily distinguishable from other sealed primary packs.

41B. This paragraph does not apply to the supply of a Schedule 8 poison by a:

(a) medical practitioner, dentist or veterinary surgeon in the practice of his or her profession;

(b) pharmacist on the prescription of a medical practitioner, dentist or veterinary surgeon;

(c) pharmacist employed at a hospital, on the written requisition of a medical practitioner, a dentist or the nurse in charge of the ward in which the Schedule 8 poison is to be used or stored; or

(d) nurse on the direction in writing of a medical practitioner or dentist.

2.4 SUSDP, PART 5

2.4.1 EUCALYPTUS AND MELALEUCA OIL

PURPOSE

The Committee considered a proposal seeking to amend the Standard Statements in Appendix E, Part 2 required for eucalyptus oil and melaleuca oil.

BACKGROUND

Standard Statements in Appendix E of the SUSDP were reviewed by a Working Party (WP) of the National Drugs and Poisons Schedule Committee (NDPSC) in 2000 for consistency with currently accepted clinical best practice in first aid, and to simplify the entries. The NDPSC adopted the revised Standard Statements recommended by this WP at its February 2001 meeting. The new standard statements specified in Appendix E for eucalyptus oil and melaleuca oil were as follows (date of effect - 31 August 2003):

A - For advice, contact a Poisons Information Centre (Phone eg Australia 13126; New Zealand 03 4747 000) or a doctor (at once).
G1 - Urgent hospital treatment is likely to be needed. (Note - the words 'at once' to be added to instruction A)."
G3 - If swallowed, do NOT induce vomiting."

The old standard statements in Appendix E for eucalyptus oil and melaleuca oil were:

"(i) If poisoning occurs get to a doctor or hospital quickly. (c) If swallowed do NOT induce vomiting. Give a glass of water."

DISCUSSION

A joint submission was received from the XXXXXXXXX and XXXXXXXXX proposing that Standard Statement G1 be deleted from the Appendix E, Part 2 entries for eucalyptus oil and melaleuca oil. The applicants stated that they objected to the statement "Urgent hospital treatment is likely to be needed" as it implied to consumers that these oils were highly toxic and that the patient would need to be rushed to the hospital for urgent treatment. The applicants also raised the point that the removal of G1 was consistent with the approach taken for other essential oils such as basil oil, bay oil,

cajuput oil and marjoram oil. The Committee noted the following points raised by the applicants:

Eucalyptus Oil

- Eucalyptus oil was not highly toxic, given the oral LD_{50} of 2480 mg/kg (rat) specified in XXXXXXXXX extensive reports provided to the Essential Oils Working Party in February 1999 and June 1999 was similar for humans. On this basis, it was proposed that eucalyptus oil should fall within the acute oral toxicity limits specified for Schedule 5 poisons, not Schedule 6. XXXXXXXXX also cited numerous scientific papers on poisoning by eucalyptus oil, which showed that the majority of patients showed nil, or only minor effects not requiring hospital treatment where close observation at home sufficed.

  An extensive study of eucalyptus oil poisoning undertaken by Webb and Pitt (1993) at Mater Misericordiae Children's Hospital (Qld) identified 41 cases of eucalyptus oil poisoning, of which 33 (80%) were "asymptomatic at home by parental report and all of these were free of clinical signs on examination in the emergency department".

- Eucalyptol (synonym:1,8-cineole) was given GRAS ("Generally Recognised As Safe") status by the Flavour and Extract Manufacturers Association (FEMA, 1965) and approved for food use by the Food and Drug Administration (FDA) of the USA.

  (Secretariat Note: The British Pharmacopoeia 2001 specifies the following components in eucalyptus oil: a-pinene: 2 to 8 per cent, b-pinene: less than 0.5 per cent, a-phellandrene: less than 1.5 per cent,limonene: 4 to 12 per cent, 1,8-cineole: not less than 70 per cent, camphor: less than 0.1 per cent.)

- Chronic toxicity, carcinogenicity and genotoxicity studies showed that 1,8-cineole did not show any such effects.
- It appeared incongruous to require a G3 statement only for a number of truly toxic and very dangerous compounds such as hydrofluoric acid (Schedules 6 and 7), formaldehyde and methanol (which causes blindness), whilst the relatively safe eucalyptus oil also required the G1 statement.
- Australia was the only country in the world that considered eucalyptus oil highly toxic and warranted scheduling as a poison. In the process of harmonisation with European countries, Australia, the home of eucalypts, would be completely out of step with the world on this point.

Melaleuca Oil

- Melaleuca oil has a chemical composition which is very close to that of marjoram oil, eg terpinen-4-ol: up to 36%, α-pinene, γ-terpinene and 1,8-cineole: up to 11%, cf. (S.G.Deans et al., Journal of Essential Oil Research, 3,341 1991).

  Secretariat Note: The following components were specified in the monograph for tea tree oil in the European Pharmacopoeia 4th Edition (2002):

α-pinene: 1-6%, α-terpinene: 5-13%, limonene: 0.5-4.0%, cineole: <15%, γ-terpinene 10-28%, ρ--cymene: 0.5-12%, terpinen-4-ol: minimum 30%, α-terpineol: 1.5-8%.

- The Council of Europe (1981) included tea tree in the list of plants and parts thereof that are temporarily acceptable for use in food [Reference: Council of Europe (1981) Flavouring Substances and natural Sources of Flavouring].

- Melaleuca oil should be treated in the same way as marjoram oil, which required only A and G3 statements.

The expert member who evaluated the XXXXXXXXX submission did not support the joint proposal to amend the Appendix E, Part 2 entries for eucalyptus oil and melaleuca oil on the following grounds:

- An oral LD_{50} value of 2480 mg/kg (rat) from XXXXXXXXX reports to the Essential Oils Working Party in February 1999 was quoted in support of the applicants' proposal. However, lower literature LD_{50} values for eucalyptus oil such as 1560 mg/kg (oral/ rat) (Brownlee G, 1940. QJl Pharm. Pharmac, 13, 130)[1] and probable lethal dose of 0.05 mL/kg to 0.5 mL/kg (human, adult) were not referred to.
- The submission quoted Webb and Pitt (1993) "Seventy seven per cent of children were symptomatic[2] despite several large ingestions….The authors consider that prudent management of cases where estimated volume ingested is large…..should include gastrointestinal decontamination using charcoal and sorbitol…". This suggested that 23% were asymptomatic[3] and that a number of these would require medical assessment/management.
- A relatively recent review of eucalyptus oil (James Magarey, Victorian PIC, 1997) stated "Careful gastric lavage and installation of activated charcoal or colonic washout should only be attempted under general anaesthesia.….The efficacy of activated charcoal in eucalyptus oil poisoning is yet to be proved".
- The acceptance by other food authorities of small amounts of eucalyptus oil as a food additive was not relevant to the consideration of the acute toxicity from ingestion of significant volumes of eucalyptus oil.
- The new First Aid Instructions (FAI) for eucalyptus oil and melaleuca oil include an encouragement to contact the PIC **before** travelling to a medical facility but alerting a parent/victim that ingestion of the oil could be serious and that medical attention may be needed (approx. 1 in 4 cases). For ingestion of significant volumes, gut decontamination under carefully controlled conditions may be indicated. On this basis, it was recommended that FAI statements A, G1 be retained for eucalyptus oil and melaleuca oil.

[1] Inclusion of the reference was agreed to at the June 2004 NDPSC Meeting (Item 1.5.1)

[2] "symptomatic" was corrected to read "asymptomatic" at the June 2004 NDPSC Meeting (Item 1.5.1)

[3] "asymptomatic" was corrected to read "symptomatic" at the June 2004 NDPSC Meeting (Item 1.5.1)

The Committee noted the result of a study on unintentional paediatric eucalyptus oil poisoning undertaken in Victoria in 1997 (Australian and New Zealand Journal of Public Health 1997, Day *et al*, Vol 21 No. 3, 297-302). The study suggested that eucalyptus oil was one of the leading poisoning agents in Victoria among the under 5 year-olds, based on approximately 77% of admissions to the Royal Children's Hospital in Melbourne for poisoning between 1988-1992 which were attributed to eucalyptus oil ingestion. These findings were also supported by data from the XXXXXXXXX which indicated that 63% of children (2532 cases between 1989-1993) presenting to emergency departments for eucalyptus oil ingestion were admitted, compared with 47% of all those presenting for poisoning in this age group, suggesting higher severity for eucalyptus oil.

The XXXXXXXXX advised that a total of 879 calls had been received relating to ingestion of eucalyptus oil, and 294 calls were received involving melaleuca oil between 1998 to 2002. However, it was indicated that no information on the outcomes of these calls could be made available due to the limitations on the way information was recorded. The XXXXXXXXX indicated that it did not support the removal of Standard Statement G1 but suggested that this may be amended to "Urgent hospital treatment may be needed".

XXXXXXXXX, XXXXXXXXX and XXXXXXXXX put forward submissions to the NDPSC seeking the right to comment further when more information about the scheduling proposal became available.

OUTCOME

The Committee agreed that the requirement for Standard Statements A, G1 and G3, for eucalyptus oil and melaleuca oil in Appendix E, Part 2 of the SUSDP remained appropriate. This decision was made on the basis of available data which supported the need to retain on product labels, a direction for consumers to contact the PIC **before** travelling to a medical facility, whilst alerting that ingestion of the oil could be serious and medical attention may be needed.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

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

3.1 VIRGINIAMYCIN

PURPOSE

The Committee considered post meeting comment in relation to the scheduling of virginiamycin.

BACKGROUND

The scheduling of virginiamycin was considered at the February 2003 meeting where it was included in Schedule 4 for all uses. This decision was based on advice received from the Expert Advisory Group on Antimicrobial Resistance (EAGAR) that continued unrestricted use poses an unacceptable risk to human health from the development and transfer of organisms resistant to this class of antibiotics in food animals. The Committee also noted that the inclusion of virginiamycin in Schedule 4 of the SUSDP would be consistent with the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) Recommendation 6.

DISCUSSION

The Committee noted the post-meeting correspondence received from XXXXXXXXX, XXXXXXXXX, XXXXXXXXX and XXXXXXXXX who all objected to the inclusion of virginiamycin in Schedule 4 of the SUSDP for all uses. The following points were raised in their submissions:

- As feed companies come under increasing pressure to control and treat acidosis, veterinarians who are less-skilled in the treatment of acidosis will be used to fulfil the prescription requirement, thus creating grounds for less prudent use of virginiamycin.
- Inclusion of virginiamycin in Schedule 4 will raise serious animal health and welfare concerns in relation to remote area grain feeding of sheep and cattle. Due to limited access to veterinarians in remote areas, the professional intervention required to satisfy the prescription of a Schedule 4 compound may not always be available.
- As there are still antibiotics available outside of Schedule 4, these may be used in place of virginiamycin to avoid the cost of engaging a veterinarian. This could have undesirable consequences for animal health and welfare as well as undesirable impacts in food residues or transfer of antibiotic resistance.
- Virginiamycin is the only compound approved for, and recognised to be effective in, the prevention of lactic acidosis in ruminants. Ionophores are not registered nor are they widely used for this purpose. The only open seller registered for acidosis prevention is sodium bentonite, which is a buffering agent.
- Virginiamycin presents a negligible human health risk when used in animals with regard to toxicology, food residues and the risk and impact of transferable antibiotic resistance.
- Oral use in cattle and sheep is not likely to promote resistance in staphylococci and streptococci.
- Recent Australian studies have demonstrated no resistance to quinupristin-dalfopristin (QD) in human clinical isolates.
- It is exceedingly unlikely that virginiamycin resistance could occur in vancomycin resistant *E.faecium* in cattle as adult cattle rarely carry *E.faecium*. Avoparcin, which

may have generated vancomycin resistant *E.faecium*, has not been used for 3 years in Australia.

- Animals kept on farms during drought periods are either breeding stock or wool sheep, neither of which can be considered an imminent threat to public health.
- Availability of virginiamycin in small pack sizes would increase the cost per unit of virginiamycin, thereby discouraging its use as a growth promotant.
- A request was made to harmonise the effective date of the rescheduling of all animal use antibiotics, rather than in a staged approach as published in the NDPSC minutes from the October 2002 meeting.

The post-meeting comment received was referred to the Australian Pesticides and Veterinary Medicines Authority (APVMA) and the EAGAR for comment.

The EAGAR advised that it stands by its original advice that virginiamycin should be Schedule 4 for all uses based on the fact that the human analogue, quinupristin-dalfopristin (QD), is an antibiotic of last resort in human medicine and is itself under strict control of use. Furthermore, the EAGAR reiterated the JETACAR recommendation that veterinarians need to take professional responsibility for the use of valuable antibiotic products that have significant implications for human health. Whilst understanding the arguments put forward by XXXXXXXXX, XXXXXXXXX, XXXXXXXXX and XXXXXXXXX, the EAGAR did not believe that there will be any major difficulties in managing cattle or sheep during times of drought resulting from the inclusion of all uses of virginiamycin in Schedule 4. The proposal that small pack sizes should be accommodated outside of Schedule 4 was not supported by the EAGAR as they may still be subject to significant misuse. The assertion that there are errors in the EAGAR risk assessment or that conclusions are unfounded, including those relating to cattle was rejected by the EAGAR. The proposed delay in the implementation of the scheduling to accommodate subsequent decisions about other antibiotics was also not supported by the EAGAR.

The APVMA considered the post-meeting submissions and notes that the EU has banned the use as feed additives of four antibiotics, including virginiamycin. Pfizer Animal Health and Alpharma challenged this regulation at the European Court of Justice in 2002, however the court concluded that the EU council's decision to ban was justified in the interest of protecting human health. The APVMA underlined that the EAGAR assessment has highlighted the hazard that a reservoir of resistance genes from exposure to virginiamycin within the animal population poses for humans on the basis of qualitative risk analysis. Thus, the justification for restricting the availability of virginiamycin is that bacterial resistance to the antibiotic might be transferred to humans ie in the interest of protecting health. The APVMA indicated that it supports the Committee's decision to include virginiamycin for all uses in Schedule 4 of the SUSDP on the basis of EAGAR's recommendation. Additionally, the APVMA advised that despite the claims that there will be difficulties in accessing virginiamycin through veterinary prescription in remote areas, the APVMA would be willing to consider an application on a case-by-case basis and issue a permit as appropriate. This permit would be in relation to the duration of administration, not the supply of the product.

The Committee noted that the APVMA had extended the deadline to comment on the draft virginiamycin report until 31 July, 2003.

The Committee took into account the EAGAR's and the APVMA's advice in conjunction with the further public submissions received under regulation 42ZCZ of the *Therapeutic Goods Regulations 1990* as part of its overall consideration of the scheduling of virginiamycin under section 52E of the *Therapeutic Goods Act 1989*.

A Member refuted the argument that animals kept during periods of drought are not for breeding stock or wool production. As these animals may be slaughtered for food consumption at a later date, the risk of transfer of antibiotic resistance to humans remains a concern.

XXXXXXXXX informed the Committee that ionophores were neither registered for the prevention of lactic acidosis in ruminants nor were they considered effective for this purpose. The Committee acknowledged that the original statement concerning the use of other Schedule 5 substances, including some Ionophores, for the treatment of feed-related acidosis was incorrect.

Members noted that no feedback had been received as a result of the timetable for the consideration of antibiotic scheduling as published in the minutes from the October 2002 NDPSC meeting. The Members agreed that decisions made regarding antibiotics would carry the same effective date as other decisions made at those meetings and there would be no delay in the implementation date of the virginiamycin scheduling decision.

A Member noted that although sale in small pack sizes would increase the cost of virginiamycin per unit, this would not sufficiently deter misuse of the substance. Another Member argued that potential resistance to QD was a key issue and extreme caution should be applied to any decision relating to this, based on the fact that QD is an antibiotic of last resort in human medicine and that it was itself under strict control of use.

The Committee's concerns regarding the potential risk for resistance to virginiamycin, and subsequent resistance to QD, were not allayed by the arguments provided in the post-meeting submissions. The Committee considered that use of virginiamycin outside of Schedule 4 did not carry a low and acceptable risk of promoting antibiotic resistance and therefore agreed that such use could not be maintained. Both the APVMA, which is the relevant authority for the registration of veterinary products, and the EAGAR, which was established by the Commonwealth Government to provide expert advice on antibiotic resistance and related matters, supported the Committee's decision to include virginiamycin in Schedule 4 of the SUSDP. Inclusion of virginiamycin in Schedule 4 is also consistent with JETACAR Recommendation 6 "that all antibiotics for use in humans and animals (including fish) be classified as Schedule 4 (prescription only)" where the risk of promoting antibiotic resistance as a non-prescription product is unacceptable.

DECISION 2003/38 - 1, Confirmation of DECISION 2003/37 - 13

In accordance with sub-regulation 42ZCZ(3), the Committee confirmed the inclusion of virginiamycin for all uses in Schedule 4 on the basis that:

- Based on available evidence, the benefits associated with unrestricted use of virginiamycin as growth promotant, and in the prevention of lactic acidosis in food producing animals, did not outweigh the risks to human health posed by the potential development of resistance to virginiamycin and cross-resistance to pristamycin and quinupristin-dafopristin (QD). QD is an antibiotic of last resort in human medicine.
- The current pattern and extent of use of virginiamycin as unrestricted veterinary medicine is expected to increase the potential for development of resistance to virginiamycin and cross-resistance to pristamycin and QD to occur.
- Inclusion of virginiamycin in Schedule 4 should ensure that the substance is used judiciously and appropriately through intervention by a veterinarian thus, limiting the potential for abuse or misuse.

Schedule 4 - Amendment

VIRGINIAMYCIN – amend entry to read:

VIRGINIAMYCIN.

Schedule 5 – Amendment

VIRGINIAMYCIN – delete entry.

Secretariat Note:

A facsimile submission of 17 June 2003 was received from XXXXXXXXX acting on behalf of XXXXXXXXX. However, the XXXXXXXXX submission was received after the June Meeting had deliberated this item and had made its final decision in relation to the scheduling of virginiamycin under sub-regulation 42ZCZ(3).

3.2 BACITRACIN

PURPOSE

The Committee considered post meeting comment in relation to the scheduling of bacitracin.

BACKGROUND

The scheduling of bacitracin was considered at the February 2003 Meeting where it was included in Schedule 4 for all uses. This decision was based on advice received from the Expert Advisory Group on Antimicrobial Resistance (EAGAR) that scheduling bacitracin outside of Schedule 4 would pose an unacceptable risk of promoting antimicrobial

resistance as it would raise the likelihood of escalating resistance when used therapeutically in animals in an unregulated/non-prescription manner. Bacitracin was listed by the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) as a category A antibiotic (essential antibiotics for treatment or prevention of animal infections where there are few or no alternatives for many infections) for meat chickens and layer hens for prevention of necrotic enteritis.

DISCUSSION

The Committee noted the post-meeting correspondence received from XXXXXXXXX objecting to the inclusion of bacitracin in Schedule 4 of the SUSDP for all uses. XXXXXXXXX stated that bacitracin was not used as a growth promotant per se and, as poultry companies have their own veterinarians or use consultant veterinarians when addressing the issue of prevention of necrotic enteritis, the use rates of bacitracin will not change as a result of the change in scheduling. XXXXXXXXX believed that this negated the EAGAR's conclusion that continued use as a growth promotant will compromise its effectiveness, as usage levels will remain the same. XXXXXXXXX also stated that they consider the issue of the application of a substance a matter for the Australian Pesticides and Veterinary Medicines Authority (APVMA), not the NDPSC. XXXXXXXXX argued that bacitracin meets the three JETACAR requirements for antibiotics that will not pose a hazard when used at levels and durations similar to "growth promotion", that is: efficiency under Australian conditions; it is not considered an important antibiotic for human use; and any evidence of cross-resistance to other antibiotics is dismissed as equivocal.

XXXXXXXXX's post-meeting comment was referred to both the EAGAR and the APVMA for comment. The EAGAR noted the points raised by XXXXXXXXX and acknowledged that bacitracin fulfils the criteria for use under Recommendation 1 of the JETACAR report. However, the EAGAR maintained that all uses of bacitracin should be Schedule 4 as it is a JETACAR rated A agent for treatment and prophylaxis of necrotic enteritis in poultry. The EAGAR was of the view that as the development of resistance to bacitracin would have a significant impact on veterinary medicine, the risk cannot be classified as acceptable. While the EAGAR noted the sponsor's assertion that the rescheduling of bacitracin will not change the volume of use, it considered that this could only be determined by active surveillance. The EAGAR also indicated it was aware of the relative roles of the NDPSC and the APVMA and highlighted that if there was a change in indication for the use of bacitracin, this would be reviewed by the APVMA.

The APVMA considered the post-meeting comment received from XXXXXXXXX and also concluded that the use of bacitracin outside of Schedule 4 posed an unacceptable risk of promoting antimicrobial resistance and would raise the likelihood of escalating resistance when used therapeutically in animals. The APVMA believed that the restriction of bacitracin to veterinary prescription only would ensure its prudent and responsible use, which is an integral part of good veterinary practice. Furthermore, the APVMA considered it was unlikely that the continued availability of bacitracin as a Schedule 6 product would uphold this principle which would minimise selection of resistant antimicrobial organisms. The APVMA noted that the Committee's decision to

include bacitracin in Schedule 4 for all uses was consistent with the JETACAR Recommendation 6 "That all antibiotics for use in humans and animals (including fish) be classified as Schedule 4 (prescription only)". Finally, the APVMA was of the view that the use rate in the poultry industry would decrease with time, since veterinary intervention calls for an accurate and thorough diagnosis to be made before a prescription is issued.

Members acknowledged that the rescheduling of bacitracin may not change the usage levels of the substance in the short-term, however including it in Schedule 4 of the SUSDP conveys a message that the use of bacitracin as a growth promotant is not appropriate.

The Committee noted that there were 5 registered products on PUBCRIS containing bacitracin or zinc bacitracin. All products, including XXXXXXXXX and XXXXXXXXX, are currently labelled as Schedule 4 (Prescription Animal Remedy), and as highlighted previously, poultry companies have their own veterinarians or use consultant veterinarians when addressing the issue of prevention of necrotic enteritis. Therefore, there would be no regulatory impact arising from the decision taken at the February 2003 meeting to include bacitracin in Schedule 4 of the SUSDP for all uses.

DECISION 2003/38 - 2, Confirmation of DECISION 2003/37 - 14

The Committee confirmed the inclusion of bacitracin for all uses in Schedule 4 on the basis that:

- Bacitracin is JETACAR rated A agent, an essential antibiotic for treatment or prevention of animal infections, where there are few or no alternatives for many infections, and the potential impact of resistance development to this valuable veterinary medicine is considered an unacceptable risk.
- The current pattern and extent of use in the treatment and prophylaxis of necrotic enteritis in poultry may lead to an increase in the potential for resistance to develop if allowed continued availability outside Schedule 4. Veterinary intervention should ensure appropriate and judicious administration of bacitracin and ensure that the substance is not misused or abused.
- Use of bacitracin requires on-going professional veterinary management.

Schedule 4 – Amendment

BACITRACIN – amend entry to read

BACITRACIN.

Schedule 6 – Amendment

BACITRACIN – delete entry.

3.3 HYALURONIC ACID

PURPOSE

The Committee reconsidered the wording of the Schedule 4 entry for hyaluronic acid agreed at the February 2003 meeting.

BACKGROUND

The February 2003 NDPSC meeting amended the Schedule 4 entries for collagen, hyaluronic acid and polylactic acid to include preparations for implantation. However, the amended entry for hyaluronic inadvertently excluded 4 veterinary products containing sodium hyaluronate for the treatment of non-infectious joint diseases (synovitis) of horses.

XXXXXXXXX drew the Secretariat's attention to this oversight and sought reinstatement of injectable products for veterinary use in Schedule 4.

DECISION 2003/38 - 3, Erratum: Correction to Decision 2003/37 – 24

The Committee recognised that the consequential regulatory impact on the Schedule 4 veterinary products was unintended and noted that the products required veterinary intervention and should therefore remain in Schedule 4. The Committee agreed that the amendment relating to the Schedule 4 entry for hyaluronic acid which was published in the February 2003 post-meeting gazette notice should be corrected accordingly and included in SUSDP 18 Amendment 1.

Schedule 4 – Amendment

HYALURONIC ACID - correct entry to read:

HYALURONIC ACID AND ITS POLYMERS in preparations for injection or implantation:

(a) for tissue augmentation;

(b) for cosmetic use; or

(c) for the treatment of animals.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 ROTENONE, DERRIS AND CUBÉ

PURPOSE

The Committee considered the foreshadowed inclusion of rotenone, derris and cubé in Schedule 6 of the SUSDP, with an appropriate cut off to Schedule 5 and exempt.

BACKGROUND

Rotenone (1,2,12,12a-tetrahydro-2-α-isopropenyl-8,9-dimethoxy-benzopyrano [3,4-b] furo [2,3-h] [1] benzopyran-6[6ah]-one) is a naturally occurring chemical with insecticidal and piscicidal properties. It is obtained from the roots of tropical and subtropical plant species from the genera Derris (tuba or derris) and *Lonchocarpus* (cubé or timbo) but also from *Tephrosia*, *Milletia*, *Mundulea*, *Spatholobus*, and *Pachyrhizus*. Rotenone was available in a wide range of purities, from powdered plant root containing around 5% rotenone to the purified technical material at up to 95% pure. Rotenone was not scheduled.

The October 2002 NDPSC meeting considered the scheduling of a product, XXXXXXXXX containing 405 g/kg magnesium fluorosilicate, 250 g/kg sulfur and (200 g/kg cubé/derris) to give 13g/kg rotenone for control of lice, ked, itchmite and mycotic dermatities in sheep. Based on the magnesium fluorosilicate content in the formulation, XXXXXXXXX fell under Schedule 6 of the SUSDP. However, the CPAS evaluation report for the product considered at the October 2002 meeting also recommended that the Committee consider the inclusion of rotenone in Schedule 6 of the SUSDP based on its toxicological profile, with a cut-off to accommodate products containing the active ingredient. Accordingly, the Committee agreed to foreshadow the consideration of the scheduling of rotenone, derris and cubé at the June 2003 meeting and that wider consultation would be undertaken prior to any scheduling action.

DISCUSSION

The Committee noted the following pre-meeting submissions received:

- XXXXXXXXX advised that it marketed two products containing rotenone: XXXXXXXXX and XXXXXXXXX. Both products were combination products and were already included in Schedule 6 because of other ingredients in the formulation, and would therefore be unaffected by the proposed inclusion of rotenone in Schedule 6. However, XXXXXXXXX suggested that products containing up to 2% (or more if toxicity indicated) should be included in Schedule 5.
- XXXXXXXXX wrote on behalf of XXXXXXXXX and XXXXXXXXX. They advised that both companies marketed household and garden products containing rotenone, which were exempt from scheduling. The XXXXXXXXX products each contained 7.5 g/kg rotenone and XXXXXXXXX contained 10 g/kg rotenone, all formulated in talc-based dusts. All products were packed in shaker packs with maximum 500 g pack sizes. The submission stated that if an LD_{50} of 130 mg/kg for

rotenone in rats was taken as an example for an acute toxicity figure, then a 10kg child would need to consume approximately ¼ of a full 500 g pack to obtain a potentially toxic dose of approximately 1300 mg. As the products could be shaken from the packs through small holes and the talc is very fine and unpalatable dust, then it was unlikely that a significant amount of dust could be consumed at the one time, even by the persistent child.

Both companies requested that rotenone in dust formulations be made exempt from the requirements of scheduling at levels below 15 g/kg, especially when access to the dust was limited by packaging. XXXXXXXXX noted that liquid formulations containing rotenone tended to contain other pesticides which resulted in an overall classification of the products in Schedule 5 or Schedule 6, therefore inclusion of rotenone in these Schedules for liquid formulations would have little effect on existing labelling. These liquid formulations were marketed in large commercial pack sizes, which would also allow exposure to significant quantities of rotenone.

- The XXXXXXXXX. raised the following points:
  - The organic industry was well aware of the toxicity levels of some naturally occurring substances, and organic operators were careful in their use of such substances.
  - Whilst rotenone was used for the treatment of parasites in the organic livestock industry, it was not widely used in organic horticulture. However, some growers continue to use it but with care.
  - The XXXXXXXXX an organic certifying body accredited by AQIS, made the following comments:
    * XXXXXXXXX containing 15 g/kg rotenone from derris was permitted for use as a parasiticide on animals in the organic industry. The animals treated with XXXXXXXXX were quarantined from sale for a minimum of 3 weeks after use.
    * In relation to other uses on vegetable products, derris was not widely used. However, XXXXXXXXX doubted that there was sufficient justification to warrant placing rotenone in Schedule 5 or 6, a view also shared by XXXXXXXXX.
- XXXXXXXXX advised XXXXXXXXX that it had ceased manufacturing and marketing XXXXXXXXX branded products containing rotenone approximately 5 years ago. This decision was taken on review of the toxicology of the said product range.

The Committee noted that there was insufficient data available at the meeting on which to base appropriate cut-offs to Schedule 5 or to exempt, as foreshadowed at the October 2002 meeting. Members indicated that there may be grounds to support the exemption of solid or semi-solid preparations containing 2% or less of rotenone based on the CPAS evaluation report. The report stated that "Although the toxicological hazards from rotenone are significant, there are several factors that can mitigate the risk of rotenone toxicity. It is practically insoluble in water, impairing absorption. It irritates mucous membranes, provoking vomiting if ingested and coughing/sneezing if inhaled, reducing the potential for absorption. It decomposes rapidly when exposed to light and air to less

toxic oxidation products. The XXXXXXXXX in their Poisons Information Monograph on rotenone stated that it is a very safe compound when properly used." The approach of exempting solid or semi-solid preparations containing 2% or less of rotenone was not expected to have a regulatory impact on existing products on the market.

A search of the PUBCRIS database yielded 23 products containing rotenone, of which 3 were unscheduled cockroach baits (mixture of sugar, rotenone and flour granules) containing 1.9% (19g/kg) rotenone. All other products including those labelled as Schedule 5 and 6 contained less than 1.9% rotenone.

The Committee preferred the approach of expressing the schedule entry in terms of rotenone content rather than on the basis of the plant material, i.e. derris and cubé, which could contain varying amounts of rotenone. Furthermore, the Committee also agreed to only include rotenone in Schedule 6, and cross-reference derris and cubé to rotenone in the index of the SUSDP. This was made on the basis that rotenone was regarded as the 'active' from a registration point of view and as such was the substance name reflected on product labels.

DECISION 2003/38 - 4

The Committee agreed to include rotenone in Schedule 6 of the SUSDP based on the toxicological profile of the substance. In addition, the Committee was of the view that there were no toxicity issues expected from preparations containing 2% or less of rotenone provided they are formulated as solid or semi-solid preparations to reduce the potential for ingestion of large amounts, particularly by children. On this basis, the Committee also agreed to exempt solid or semi-solid preparations containing 2% or less of rotenone from the requirements of scheduling.

Schedule 6 – New entry

ROTENONE **except** in solid or semi-solid preparations containing 2 per cent or less of rotenone.

4.2 CUBÉ

Refer to item 4.1

4.3 DERRIS

Refer to item 4.1.

4.4 MORANTEL

PURPOSE

The Committee considered the nomenclature for morantel tartrate.

BACKGROUND

The February 2003 meeting agreed to include morantel tartrate in Schedule 6 of the SUSDP with cut-offs to Schedule 5 and exempt, based on its acute oral toxicity. The substance was unscheduled prior to this meeting. In addition, the Committee also agreed to foreshadow the inclusion of all salts of morantel in Schedule 6 and Schedule 5 of the SUSDP for consideration at the June 2003 meeting. This was made on the grounds that all salts of morantel should be subject to the same scheduling controls, based on the available data.

DISCUSSION

The Committee noted that there was no pre-meeting submission received in relation to this item and agreed to move forward with the proposal.

DECISION 2003/38 - 5

The Committee agreed that it was appropriate to amend the entry for morantel tartrate to morantel in the SUSDP, on the grounds that all salts and derivatives of morantel should be subject to the same scheduling controls based on comparable toxicological profiles.

Schedule 6 – Amendment

MORANTEL TARTRATE – Amend entry to read:

MORANTEL **except**:

(a) when included in Schedule 5;

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

Schedule 5 – Amendment

MORANTEL TARTRATE – Amend entry to read:

MORANTEL in preparations containing 25 per cent or less of morantel **except** in preparations containing 10 per cent or less of morantel.

4.5 IVERMECTIN

PURPOSE

The Committee considered post meeting comment in relation to the scheduling of ivermectin.

BACKGROUND

Ivermectin was considered at the February 2003 NDPSC Meeting. XXXXXXXXX, the sponsor of a new product XXXXXXXXX, requested that the 2% limit included in the Schedule 5 ivermectin entry be amended to accommodate their product. The Committee agreed to include ivermectin preparations containing 3.5% or less of ivermectin in Schedule 5 of the SUSDP, however a restriction that the products must be packaged with a child-resistant closure (CRC) was included. The limit for ivermectin products packaged without a child-resistant closure in Schedule 5 remained unchanged at 2% or less.

XXXXXXXXX provided post-meeting correspondence stating that they believed that the packaging of their product complied with the definition of "child-resistant packaging" in the SUSDP.

DISCUSSION

The Committee noted that the post-meeting correspondence from XXXXXXXXX had been referred to the APVMA for consideration at registration.

XXXXXXXXX highlighted that Part 1 – Interpretation of the SUSDP defined "Child-resistant closure" as:

(a) a closure that complies with section 2 (Requirements for Reclosable packages) of Australian Standard AS 1928-2001 *Child Resistant Packages*;
(b) a closure approved by any order made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*; or
(c) in the case of a can fitted with a press-on lid, a lid of the design known as "double tight" or "triple tight".

Furthermore, it was pointed out that Part 2 – Labels and Containers – paragraph 25(2) of the SUSDP states "The manufacturer or packer of a poison must ensure that the child-resistant closure is appropriate for the container and the poison and that it retains its child-resistant properties for the expected life of the poison".

OUTCOME

The Committee concluded that it is the responsibility of the manufacturer or packer of a poison required to be fitted with a CRC to comply with these provisions.

4.6 CHLORINATING COMPOUNDS

PURPOSE

The Committee considered amending the class entry for chlorinating compounds to the Appendix F, Part 3 of the SUSDP.

BACKGROUND

The February 2003 meeting confirmed the Schedule amendments made to all chlorinating compounds entries in the SUSDP, following a review of the scheduling of these compounds. The February meeting also agreed to amend Part 2, Paragraph 7(1)(d) of the SUSDP, to provide an exemption for dry chlorinating compounds containing more than 10% of available chlorine from the required cautionary statement "**FIRE AND EXPLOSION HAZARD**", when certified by a competent authority as not being a Dangerous Good of Class 5.1. Consequential amendments were then made to Appendix E, Part 2 and the chlorinating compounds listed in Appendix F, Part 3, and of the SUSDP, for consistency with the Schedules and the new provision included in Part 2, Paragraph 7(1)(d) of the SUSDP. The above amendments have been included in SUSDP 18 Amendment 1, which was to take effect on 1 September 2003.

Following the February 2003 meeting, it was noted that whilst the consequential amendments to the Appendix F, Part 3 entries for individual chlorinating compounds were made, the class entry for chlorinating compounds in this appendix remained unchanged.

DISCUSSION

The Committee agreed that the proposed change to the Appendix F, Part 3 class entry for chlorinating compounds was originally intended as part of the consequential amendments made at the February 2003 meeting. On this basis, it was agreed that the chlorinating compounds entry in Appendix F, Part 3 be corrected and included in SUSDP 18 Amendment 1 as an erratum, in order to consolidate all the amendments relating to this class in one document and to maintain the same effective date, thereby avoiding confusion. This was considered particularly important as the amendments had implications for product labels.

A proposal was also received from XXXXXXXXX to amend Safety Direction 13 in Appendix F of the SUSDP for chlorinating compounds. However, it was subsequently withdrawn on XXXXXXXXX advice that the affected products were pool chemicals, specifically sanitisers and oxidisers, and therefore not covered by the provisions of Appendix E and F of the SUSDP.

DECISION 2003/38 - 6, Erratum: Correction to Decision 2003/37-3

The Committee agreed to correct Decision 2003/37-3 to include the consequential amendment to the chlorinating compounds entry in Appendix F, Part 3 of the SUSDP, which should have been part of the amendments made under this decision at the February 2003 meeting. Additionally, the Committee agreed to publish the corrected decision as an erratum in SUSDP 18 Amendment 1.

Appendix F, Part 3 – Amendment

Chlorinating compounds – amend entry to read:

Chlorinating compounds	Warning Statements	Safety Directions
(a) in household cleaning or bleaching preparations.	20	
(b) preparations containing less than 10 percent of available chlorine.	11	1,4,10
(c) liquid preparations containing 10 per cent or more of available chlorine.	3,18	1,4,26,8,10, 19,17,18,20, 15,16,22,6
(d) dry preparations containing 10 per cent or more of available chlorine.	22,23, 0,18	1,4,26,8, 12, 13,14,19, 17, 20,21,15,16,22
(e) dry preparations containing 10 per cent or more of available chlorine certified by a relevant State or Territory authority as not being a Dangerous Good of Class 5.1 (oxidising substances).	22,10,18	1,4,26,8, 12, 13,14,19, 17, 20,21,15,16,22
(f) compressed blocks or tablets containing 10 per cent or more of available chlorine **except** in preparations for use in toilet cisterns only, containing 15 g or less of trichloroisocyanuric acid	22,23,10	12,13,14,19, 17,18,21,15
(g) other compressed blocks or tablets containing 10 per cent or more of available chlorine certified by a relevant State or Territory authority as not being a Dangerous Good of Class 5.1 (oxidising substances) **except** in preparations for use in toilet cisterns only, containing 15 g or less of trichloroisocyanuric acid.	22,10	12,13,14,19, 17,18,21,15

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

5.1 SUSDP, PART 4

5.1.1 CREOSOTE

PURPOSE

The Committee considered an overview of creosote toxicity and uses, prepared by the Office of Chemical Safety; this overview included a summary of a draft Concise International Chemical Assessment Document (CICAD) on coal tar creosote, which was based on a comprehensive literature search performed in June 2002.

BACKGROUND

Creosote is the name used for a variety of products that are mixtures of many chemicals. Such products include wood creosote, coal-tar creosote, coal tar, and coal tar pitch. Creosotes do not occur naturally in the environment; they are created by high-temperature treatment of beech and other woods (wood creosote) or coal (coal tar creosote), or from the resin of the creosote bush (creosote bush resin).

Wood creosote (CAS 8021-39-4) is composed mainly of phenol, cresols, and guaiacol, and has been used as a disinfectant, laxative, cough treatment (expectorant), wood preservative and in cosmetics.

Coal tar creosote (CAS No. 8001-58-9), obtained by fractional distillation of crude coal tars, is the most common form of creosote in the workplace. There are 6 major classes of compounds in creosote, viz: aromatic hydrocarbons (eg. benzene, toluene, xylene and a large range of polycyclic aromatic hydrocarbons (PAHs) which can constitute up to 90% of creosote), tar acids/phenolics (e.g. cresols), tar bases/nitrogen-containing heterocycles (e.g. quinoline), aromatic amines (e.g. aniline), sulfur-containing heterocycles and oxygen-containing heterocycles (e.g. 2,3-benzofuran). The approximate distillation range is 200-400°C.It is widely used as a wood preservative, water proofing agent for structures on land, in marine and fresh waters, railway crossing timbers and sleepers, bridge and pier decking, poles, log homes, fencing and in children's playgrounds. Non-wood uses other than as a timber preservative include use as an anti-fouling agent for concrete marine pilings, animal and bird repellent, fungicide, insecticide, animal dip and treatment for psoriasis. Coal tar creosotes, coal tar and coal tar pitch are similar in composition.

Coal tar (CAS No. 8007-45-2) and coal tar pitch (67996-93-2) are by-products of the high-temperature treatment of coal to make coke and coal gas. Coal tar products are ingredients in medicines used to treat skin diseases such as psoriasis and they have also been used as animal and bird repellents, insecticides, animal dips, and fungicides.

Creosote was included in Schedule 2 for therapeutic use and Schedule 6 for other uses, on the recommendation of the Schedule Review Panel at the November 1984 meeting.

Preparations containing 3% or less of phenols were then exempt. In 1986 the exemption was modified to include homologues of phenol and the Schedule 2 entry was modified to restrict the entry to human therapeutic use. This was followed in February 1988 by a further restriction to the Schedule 2 entry to limit it to wood creosote, to differentiate it from coal creosote used as a timber preservative. At the February and May 2000 meetings, the Schedule 2 entry was amended to remove any reference to 'phenols' and an exemption of 10% or less creosote was included in Schedule 2 to harmonise with NZ. Use of the term "derived from wood" was also considered redundant and was removed, as the Martindale 31st Edition (1996) referred to creosote as wood creosote.

At the June 2002 meeting the then XXXXXXXXX member asked the committee to review the creosote entries in the SUSDP, based on the concerns relating to its carcinogenic potential and safety for use as a wood preservative. The June 2002 meeting agreed to ask the Office of Chemical Safety to review the safety of coal tar creosote for such use, and present its findings at the June 2003 meeting.

NOMENCLATURE

The Committee had used "creosote" to refer to both "wood creosote" as defined by Martindale, and "coal tar creosote" as defined in the Australian Standard AS1143-1973 - High Temperature Creosote for the Preservation of Timber.

Martindale defines creosote as wood creosote, consisting of a mixture of guaiacol, cresol, and other phenols obtained from wood tar. Coal tar creosote was not defined.

The BP 2001 defined coal tar as a product obtained from bituminous coal by destructive distillation at about 1000°C. There was no definition for creosote in BP 2001.

DISCUSSION

XXXXXXXXX from the Office of Chemical Safety prepared an overview on coal tar creosote and made a presentation to the Committee. Below is a summary of the Creosote Overview:

- Information on effects of coal tar creosote in the general population was scarce. Creosote was involved in incidental or accidental poisoning incidents mainly due to its use as a pesticide. Deaths occurred following ingestion of about 1-2 g (children) or of about 7 g (adults). Symptoms included salivation, vomiting, respiratory difficulties, vertigo, headache, loss of pupillary reflexes, hypothermia, cyanosis, convulsion, etc, accompanied by oesopharyngeal, intestinal, pericardial, liver and kidney damage.
- Most reports on the effects of coal tar creosote in humans refer to occupational exposure, resulting mainly from dermal and/or inhalation contact to creosote or creosoted wood. The most apparent effects included irritation or lesions of skin and eyes including phototoxic/photoallergic reactions, sometimes accompanied by general symptoms such as depression, weakness, headache, slight confusion, vertigo, nausea,

increased salivation or vomiting. Photosensitisation (sensitisation of the skin to UV light by creosote) was observed in exposed workers. Increased risks for lip and skin cancers were observed in cohort studies of Swedish and Norwegian wood impregnators and in Finnish round timber workers. The mortality for cancer of the scrotum was elevated among brick makers exposed to creosote. Single epidemiological studies suggested a possible risk for bladder cancer, multiple myeloma and lung cancer. Two case-control studies suggested an increased risk of brain tumours and neuroblastoma among offspring of male workers with possible creosote exposure. All the epidemiological studies were based on qualitative estimations of exposure.

- The general population may be exposed to creosote or creosote components by handling creosote or products containing creosote and by contact with creosote-contaminated air, water, soil, or food. Routes of exposure include inhalation, drinking/ingestion and skin contact. Taking into account several assumptions, exposure estimates were undertaken using benz[*a*]pyrene (BaP) as a marker substance for two important exposure scenarios:
  - A daily intake of about 2 ng BaP/kg bw had been assessed for children playing on creosoted playground equipment.
  - The daily intake of BaP from consumption of vegetables and fruits from gardens in the vicinity of plants exposed to creosote had been estimated to range from 1.4 to 71.4 μg/kg bw.

- Based on limited studies, creosotes were of low to moderate acute toxicity in experimental animals. The lowest LD_{50} value of 433 mg/kg body weight was reported in mice after oral exposure. There was little information on the effects of creosotes following short-term exposure.
- A study examining the skin carcinogenicity in mice of two samples of coal tar creosote, with different BaP contents, and BaP alone showed significant increase in papillomas and squamous cell carcinomas rate at the site of application. Other organs were not examined. A linear relationship was observed between tumour rate and the dose of BaP in the creosote solution applied to the skin. There was no evidence of a threshold for carcinogenic effects. In this study, creosote was about 5 times more carcinogenic than BaP alone.
- A number of *in vitro* tests in bacterial and mammalian systems showed creosote to be genotoxic. The pattern of genotoxicity observed was similar to that found with PAHs. Creosote was also genotoxic in an *in vivo* micronucleus test in mice. Tests with fish cells in culture showed that the cytotoxicity of creosote was enhanced by irradiation with UV light. This was consistent with the known phototoxic potential of some PAHs. Creosote was also shown to be a hepatic microsomal enzyme inducer in laboratory mammals.
- There were no adequate animal studies on reproductive or developmental toxicity of creosotes. However, creosote had been shown to elicit oestrogen-mediated activities *in vitro*, indicating some potential for endocrine disruption. Adverse reproductive effects had also been reported in fish exposed to creosote.

- Creosote is a genotoxic carcinogen, for which no safe level of exposure could be established. There was consistent evidence from human studies that creosote caused skin cancer but the studies did not allow a dose-response analysis.
- The Scientific Committee of Toxicity, Ecotoxicity and the Environment concluded the following in its opinion (revised) on cancer risk to consumers from creosote containing less than 50 ppm benzo-[a]-pyrene and/or from wood treated with such creosote and estimation of respective magnitude expressed at the 8th CSTEE plenary meeting, Brussels, 4 March 1999 (see also: http://europa.eu.int/comm/food/fs/sc/sct/out29_en.html).

  1. Given the genotoxicity of BaP and the outcome of the Fraunhofer skin painting study, there was sufficient scientific evidence to support the opinion that there was a cancer risk to consumers from creosote containing less than 50 ppm BaP and/or from wood treated with such creosote.

  2. BaP was a good indicator for the carcinogenic hazard of the creosote preparation tested, since there was a linear relationship between cancer incidence and BaP dose. However, the cancer potency of the creosote preparation was 5-fold higher than judged from its BaP content.

  3. On the basis of available information, even taking into account the considerable uncertainties in assessing the risks for children coming into contact with creosote-treated wood, the magnitude of the risk gave clear reasons for concern. However, the highest estimated exposure was some 6-30 times lower than the oral exposure of the adult population to BaP in food.

- The International Agency for Research on Cancer (IARC) determined that coal tar creosote was probably carcinogenic to humans. Skin cancer and cancer of the scrotum resulted from long exposure to low levels of these chemical mixtures, especially through direct contact with skin during wood treatment or manufacture of coal tar creosote-treated products, or in coke or natural gas factories. Cancer of the scrotum in chimney sweeps had been associated particularly with prolonged skin exposure to soot and coal tar creosote. Eating food or drinking water contaminated with a high level of creosotes may cause a burning in the mouth and throat, as well as stomach pains. Brief exposure to large amounts of coal tar creosote may result in a rash or severe irritation of the skin, chemical burns of the surfaces of the eye, convulsions, mental confusion, kidney or liver problems, unconsciousness, or even death. Longer exposure to lower levels of coal tar creosote, coal tar, or coal tar pitch by direct contact with skin or by exposure to the vapours from these mixtures could also result in sun sensitivity and cause damage to skin, such as reddening, blistering, or peeling. Longer exposures to the vapours of the creosotes, coal tar, or coal tar pitch could also cause irritation of the respiratory tract. Coal tars were classified Group 1 - Carcinogenic to humans.
- The US National Toxicology Program classified coal tar (coke oven emissions, coal tar, coal tar pitch, and creosotes) as a known human carcinogen (NTP, 1998). Coal tars and coal tar pitches were known to be human carcinogens based on sufficient

evidence of carcinogenicity in humans (IARC 1985, 1987). Pharmaceutical coal tars and tar ointments caused skin papillomas, squamous cell carcinomas, and/or carcinomas when applied to the skin of mice of both sexes.

- Some Regulatory Controls on Coal Tar Creosote:

EU

Wood treated with creosote; creosote oil; coal tar distillates; naphthalene oils; creosote oil; acenaphthalene fraction; coal tar distillates, upper; anthracene oil; crude coal tar acids; wood creosote; low temperature tar oil, alkaline, may not be placed on the market. However, preparations containing less than 0.005% by mass benzo[*]pyrene and water-extractable phenols at less than 3% by mass may be used in industrial installations or for *in situ* re-treatment by professionals (and marked as such). They must not be available to consumers and must be in >20L packs. Treated wood may not be used inside buildings, in toys; in playgrounds, parks, gardens and outdoor recreational facilities where there was a risk of frequent skin contact; in the manufacture of garden furniture; in the manufacture, use and re-treatment of containers intended for growing purposes; in packaging that may come in contact with materials destined for animal or human consumption, or in other materials which may contaminate the products listed above.

USA

The EPA classified coal tar creosote as a restricted-use pesticide ie. it could only be bought and used by certified applicators and only for those uses covered by the applicator's certification.

Australia

In the SUSDP, "creosote" was included in Schedule 6 **except**: (a) when included in Schedule 2; or (b) in preparations containing 3 per cent or less of phenols and homologues of phenol boiling below 220°C. It was included in Schedule 2 for human therapeutic use, except in preparations containing 10 per cent or less of creosote. First Aid Instructions indicated in Appendix E of the SUSDP (NEW standard statements for poisons other than those agricultural or veterinary chemicals registered by the Australian Pesticides and Veterinary Medicines Authority - APVMA) were:

A For advice, contact a Poisons Information Centre or a doctor (at once)
G3 If swallowed, do not induce vomiting.
E2 If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by the Poisons Information Centre or a doctor, or for at least 15 minutes.
S1 If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

The APVMA's MRL Standard (Maximum Residue Limits In Food And Animal Feedstuff. April 2003) listed creosote in Table 5 (substances for which maximum residue limits are not necessary). The uses for creosote covered in the Table 5 entry were "Timber treatment: - Treatment for tree trunks - Disinfectant for animal and poultry houses, egg hatcheries and associated equipment excluding dairies and milking equipment". There are 9 registered wood preservative products containing high temperature coal tar creosote, one product for use as an agricultural disinfectant (type of creosote was undefined) and three veterinary medicine for the treatment of lameness in animals (ointments/liniments containing 2% and 18% w/v coal-tar creosote) and for bloat in horses (oral preparation containing 1.7% v/v 'creosote' in a base of 47% pine tar).

- The oncogenic potential of wood creosote (, *the principal active ingredient of 'Seirogan', a herbal antidiarrhoeal medication)*. (Kuge et al, Int. J Toxicol 2001 Sep-Oct; **20**(5):297-305) was assessed in a 96/103 week oral gavage study in rats. No evidence of oncogenicity was seen at doses of up to 200 mg/kg bw/day of wood creosote, which met or exceeded the maximum tolerated dose.
- However, The European Scientific Committee on Cosmetic Products and Non-Food products Intended for Consumers (SCCNFP) published an opinion concerning the genotoxic and carcinogenic potential of wood tars and preparations (adopted at their 23rd Plenary Meeting on 18th March 2003 -Document SCCNFP/0646/03, final). The committee noted that wood tar, wood creosote, and wood oils are complex mixtures, with genotoxic PAHs (eg. chrysene, B(*a*)P]) present in varying amounts. The Committee concluded that wood tar preparations have been found to induce both benign and malignant skin tumours in mouse skin and to form DNA adducts in human skin and thus concluded that wood-tar derived products may present a risk of skin cancer when dermally applied.

The following points were highlighted in the Creosote Overview as issues for consideration:

- The SUSDP listed only "creosote". It was included in Schedule 6 except: (a) when included in Schedule 2; or (b) in preparations containing 3 per cent or less of phenols and homologues of phenol boiling below 220°C. It was in Schedule 2 for human therapeutic use, except in preparations containing 10 per cent or less of creosote. Wood creosote and coal tar creosote are very different mixtures and have different CAS numbers. (In the EC, creosote; creosote oil; coal tar distillates; naphthalene oils; creosote oil; acenaphthalene fraction; coal tar distillates, upper; anthracene oil; crude coal tar acids; wood creosote; low temperature tar oil, alkaline, are separately referenced in Annex I to Directive 76/769/EEC; wood treated with these mixtures may not be placed on the market, and these products are significantly restricted in use.)
- Coal tar creosote contains a large number of polycyclic aromatic hydrocarbons. It was noted that in liquid aromatic hydrocarbons, the SUSDP controlled total polycyclic aromatic hydrocarbon content (as measured by IP 346) at 1% or less (Schedule 7 cut-off).

- Coal tar creosote based products appeared to be freely available for domestic use in Australia. The toxicology profile of coal tar creosote would appear to be inconsistent with its general availability. It was noted that in the USA and Europe, coal tar creosote was limited to industrial use and to licensed applicators. Furthermore, in Europe, all marketed coal tar creosote preparations for use in industrial installations or for *in situ* re-treatment by professionals (to be marked as such) were required to contain less than 0.005% by mass benzo[*a*]pyrene and water-extractable phenols at less than 3% by mass.
- Coal tar products are also ingredients in medicines used to treat skin diseases such as psoriasis. In Australia, there appear to be a significant number of such products, generally containing between 2 - 5% coal tar solution; at least one XXXXXXXXX is listed as containing just coal tar. Since coal tar creosotes, coal tar, and coal tar pitch are similar in composition, containing polycyclic aromatic hydrocarbons, phenols, and cresols, the issue of whether these are appropriate human therapies should be considered.. The US FDA stated that coal tar shampoos in strengths between 0.5% and 5% were both safe and effective (10% coal tar solution is equivalent to 2% crude coal tar). However, California's Proposition 65 set the "No Significant Risk Level" (NSRL) for coal tar at 0.5%, meaning that products the FDA had deemed to be safe required a cancer warning label by Californian law.
- 'Creosote' (listed in the AAN and defined by Martindale as wood creosote) is permitted in listed medicines as a homeopathic active ingredient; there are products listed on the ARTG containing creosote in homeopathic quantities of 2X dilution and upwards (advice from the Office of Complementary Medicines). Additionally there are several products containing 'tar' (defined by the BP as bituminous liquid from the wood of various trees of the family Pinaceae), including bath oil and "Pinetarsol" preparations containing 2.3% pine tar, as well as some medicated bars and ointments/creams containing 1% polytar (made up of 30% tar BP and 30% cade oil, which is juniper tar).

The following actions were proposed in the Creosote Overview:

- That the committee consider:-

  i) the creation of a specific SUSDP entry for coal tar creosote, with entries if and as necessary for other coal tar derived mixtures, and wood creosote.

  ii) whether the marketing of coal-tar creosote as a wood preservative should be limited to industrial use and to licensed applicators.

  iii) whether all marketed coal tar creosote preparations should be required to contain limits on specific toxic and carcinogenic contaminants of concern (eg. less than 0.005% by weight of benzo[*a*]pyrene and water-extractable phenols at less than 3% by weight).

iv) the appropriateness of coal tar preparations being available for the treatment of psoriasis (and for any other cosmetic uses that may exist).

v) the appropriateness of creosote being available in oral pharmaceutical preparations.

- With respect to coal-tar creosote products registered as agricultural chemical products, concerns about the availability of these products in the domestic and home garden market need to be referred to the APVMA. Any more extensive evaluation of creosotes used as pesticides would need to be conducted through the APVMA as it was the relevant regulatory authority. Any such review would also deal with creosote-based agricultural antiseptics and veterinary medical products.
- Issues relating to the therapeutic use of tars and creosotes need to be referred to the Non-Prescription Medicines Branch (NPMB) of the TGA for evaluation and consideration. There had been some discussion at past Medicines Evaluation Committee (MEC) meetings with respect to the carcinogenicity and human safety of creosote and coal tar preparations.
- As the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) was responsible for the assessment of cosmetics, they could advise in the use of tars and creosotes in such products.
- The Office of Complementary Medicines (OCM) had advised that creosote was permitted in listed medicines only as a homeopathic active ingredient. There were products listed on the ARTG containing creosote in homeopathic quantities of 2X dilution and upwards.

The Committee discussed the following issues:

- Potential conflict in the existing SUSDP entries for creosote and liquid aromatic hydrocarbons, given that creosote was reported to contain up to 90% polycyclic aromatic hydrocarbons;
- Whilst the industrial uses for coal tar were subject to stringent regulatory controls in some countries including the United States of America (USA) and the EU, the same regulatory rigour was not applied to therapeutic uses;
- In Australia, the majority of coal tar creosote based products registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) were subject to Schedule 6 controls. However, the scope of the application of wood preservatives containing creosotes was widespread and commonly used within the home environment, e.g. treated home furniture, building materials, wooden fences, etc. On this basis, there was a significant potential for exposure by the public to creosotes;
- The need to obtain information from other regulatory agencies involved in the registration of products containing creosotes on the range and nature of products, use patterns and concentration of creosotes in such products;

- There was a need to differentiate in the SUSDP the entries for wood-derived creosote from coal-derived creosote, to reflect the significant differences in their toxicological profiles;
- Potential implications for listed medicines to be taken into account when considering a review of the scheduling of creosotes for therapeutic use;
- The need for public access to the Creosote Overview;
- Coal tar for use in cosmetics was included in Appendix C of the SUSDP therefore it was unlikely to be contained in cosmetic products;

OUTCOME
The Committee agreed to review the scheduling of creosote and related substances at the October 2003 meeting, and publish this intent in the June 2003 post- and October 2003 pre-meeting gazette notices to facilitate appropriate public consultation.

5.1.2 CASSIA OIL

PURPOSE

The Committee considered the proposal seeking to amend the cut-off for exemption in Schedule 5 from 2% to 5% of cassia oil.

BACKGROUND

Cassia oil consists largely of trans-cinnamaldehyde (60-80%), which is a severe skin irritant and sensitiser, and has an acute oral LD50 of 2.8 mL/kg (2.5-3.2 mL/g) in the rat. Although trans-cinnamaldehyde itself is highly sensitising, cassia oil is not as highly sensitising given the trans-cinnamaldehyde content. The sensitisation potential of essential oils was investigated by XXXXXXXXXX which established that certain oils, notwithstanding their content of highly sensitising compounds such as cinnamaldehyde, were not sensitising. This phenomenon was described in various literature references as 'quenching effect'.

The February 2000 NDPSC Meeting agreed to include cassia oil in Schedule 5 of the SUSDP with no cut-offs. This decision was made on the basis of the potential of cassia oil (containing trans-cinnamaldehyde) to result in human toxicity, as indicated by the acute oral toxicity in the rat, its severe irritancy and skin sensitisation potential. Because of the severe irritancy even in low concentrations, i.e 0.5%, no exemptions from scheduling for small volumes or low concentrations were considered appropriate. The Committee also agreed that a child-resistant closure was required for containers with volumes of 200 mL or less and that Safety Direction 4 (*Avoid contact with skin*) should be reflected on product labels. Whilst the Committee did not establish a cut-off in Schedule 5 at the time, it did however agree that the issue of a cut-off could be reconsidered in the event that industry provided information on additional uses which were not taken into account.

The August 2001 NDPSC meeting considered scheduling cut-offs for cassia and cinnamon oils. At this meeting, the Committee agreed that the key concern was the application of these oils to the skin and the potential for development of skin irritation or sensitisation. The Committee acknowledged that the presence of these oils at low levels in oral complementary medicines was unlikely to pose a hazard and on this basis, the Committee agreed to foreshadow the exemption of all preparations containing cassia or cinnamon oils at 2% or less from scheduling. This approach was deliberate to provide industry sufficient time to advise the Committee if there were affected products containing more than 2% of cassia or cinnamon oil. No existing product containing more than 2% of cassia oil was identified at the time, and the Committee confirmed the foreshadowed decision which was included in SUSDP 16 Amendment 4, and came into effect in 1 June 2002.

XXXXXXXXX had recently become the sponsor of XXXXXXXXX which contains 5% cassia oil and sought an amendment to the Schedule 5 entry to exempt the product.

DISCUSSION

The Committee noted the following points raised for consideration by XXXXXXXXX:

- XXXXXXXXX was a rubefacient for external topical use and approved for temporary relief of aches and pains of muscles and joints, arthritis, rheumatism and backache. The product contained 11% camphor, 10% menthol, 7% cajuput oil, 6% dementholised mint oil, 5% clove oil and 5% cassia oil in a paraffin base. The minimum lethal dose following oral and topical administration of the product was LD >8.5 g/kg of product, which greatly exceeded human therapeutic doses.
- Cassia oil was a well-recognised rubefacient; an agent that produced a mild irritation, reddening of the skin, local vasodilation and thereby increasing the blood supply to the area. On this basis, Safety Direction 4 (*Avoid contact with skin*) was inappropriate for a rubefacient and should this label requirement remain, then the product would have to be discontinued.
- XXXXXXXXX had a long history of safe use in Australia (over 20 years) and overseas, and there had been no associated reports of adverse reactions on the ADRAC database. A patch test with XXXXXXXXX on 20 volunteers were carried out under occlusive conditions. Mild irritation was reported in 1 to 3 patients with the study concluding that the medicament should be safe when applied on the skin with no dressing. Skin sensitisation was not a likely problem with the preparation, and animal studies showed that XXXXXXXXX caused only minor dermal irritation in the rat and guinea pigs, and did not cause delayed hypersensitivity reactions such as phototoxicity and photosensitisation. However, the product did cause marked irritation to rabbit skin under occlusive dressing and to rabbit eyes.
- In the period 1991 to May 2002, the manufacturer received no adverse event reports for XXXXXXXXX and a total of 4 allergic reactions reports for XXXXXXXXX were received from 3 countries.

- No new risks had been identified during the safety review. However, the advice that medical attention should be sought if relief was not obtained after 2 weeks had been added to the Summary of Product Characteristics (SPCs).
- XXXXXXXXX containing 5% cassia oil, which had been registered on the ARTG since March 1998, had been overlooked at the time of scheduling of cassia oil.

The ADRAC Unit confirmed that there had been no adverse report associated with cassia oil on the ADRAC database.

The Committee noted that there was no product listed on the PUBCRIS database containing cassia oil. However, there may be one listed product on the ARTG that could contain 100% cassia oil XXXXXXXXX for topical use (entry on ARTG was unscheduled) and another listed product for oral use XXXXXXXXX which may contain 6.6% cassia oil (entry was also unscheduled).

It was noted that XXXXXXXXX was indicated and approved for use as a rubefacient and members recognised that labelling the product with Safety Direction 4 (*Avoid contact with skin*) was inappropriate, as pointed out by the applicant. The Committee was of the view that its concern regarding the irritant property of cassia oil would not be relevant to rubefacient products, where such a characteristic was essential for therapeutic effect.

A member recalled that when the scheduling of cassia oil was considered by the Essential Oils Working Party in August 2001, the use of cassia oil as a rubefacient was not raised in any of the submissions received during public consultation. Whilst members supported the exemption of the XXXXXXXXX from scheduling, it was agreed that there was a need to limit the amendment in Schedule 5 and exempt only rubefacient dermal preparations containing 5% or less cassia oil, so preparations for other uses would not be inadvertently exempted from scheduling without further data.

DECISION 2003/38 - 7

The Committee agreed to exempt cassia oil in rubefacient dermal preparations containing 5% or less of cassia oil from the requirements of scheduling. Based on the available data, the Committee took into account the following points in its consideration:

- long history of safe use of rubefacient dermal preparations containing 5% cassia oil in Australia;
- the symptoms for which the product was indicated could be diagnosed by the consumer without assistance from a pharmacist or medical practitioner;
- the treatment could be managed appropriately by the consumer;
- the concern in relation to the irritant property of cassia oil was not relevant to products approved for use as rubefacient containing up to 5% cassia oil; and
- there were no toxicity issues expected from unrestricted use of rubefacient dermal preparations containing 5% or less of cassia oil.

Schedule 5 - Amendment

CASSIA OIL – Amend entry to read:

CASSIA OIL **except**:

(a) in food additives;

(b) in preparations for dermal use as a rubefacient containing 5 per cent or less of cassia oil; or

(c) in other preparations containing 2 per cent or less of cassia oil.

5.2 SUSDP, PART 5

5.3 WARNING STATEMENT AND GENERAL SAFETY DIRECTIONS ESTABLISHED BY CPAS FOR AGRICULTURAL AND VETERINARY CHEMICALS (STANDING AGENDA ITEM).

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

6.1 AZIMSULFURON

PURPOSE

The Committee considered the scheduling of the new active constituent, azimsulfuron.

BACKGROUND

XXXXXXXXX provided data in support of the approval of the new TGAC, azimsulfuron and registration of the new product, XXXXXXXXX, containing 500 g/kg azimsulfuron. XXXXXXXXX

Azimsulfuron is a sulfonylurea herbicide which is structurally related to bensulfuron-methyl. The mode of action of sulfonylureas is by inhibition of acetolactate synthase, a key enzyme in the synthesis of several amino acids in plants. Bensulfuron-methyl for agricultural use was listed in Appendix B in August 1987 based on low toxicity.

DISCUSSION

[Paragraphs deleted]

The main toxicological hazards identified were slight eye irritation for azimsulfuron and slight eye and skin irritation observed for XXXXXXXXX. CPAS considered that these slight effects would be adequately addressed by appropriate safety directions on the

product label, and recommended exemption of both the active ingredient and the product from the requirements of scheduling.

DECISION 2003/38 - 8

The Committee agreed to exempt azimsulfuron for agricultural use as a herbicide from scheduling requirements based on its low toxicity profile and list the substance in Appendix B of the SUSDP.

Appendix B – New Entry

AZIMSULFURON……..June 2003……..a……..1.1

6.2 GAMMA-CYHALOTHRIN

PURPOSE

The Committee considered the scheduling of a new active constituent, gamma-cyhalothrin.

BACKGROUND

XXXXXXXXX submitted data in support of the approval of a new active constituent, gamma-cyhalothrin, which is the purified active isomer of the already approved cyhalothrin and lambda- cyhalothrin. Registration was also sought for the new product in a capsule suspension formulation, XXXXXXXXX, containing 150 g/L of gamma-cyhalothrin, for use in controlling a variety of insect pests on pasture and crops including cotton, barley, wheat, soybeans and peas.

Gamma-cyhalothrin, cyhalothrin and lambda-cyhalothrin have the same chemical structure. They differ only in the composition of the stereoisomers present. Cyhalothrin is comprised of 4 stereoisomers (1R, cis, Z-S; 1S, cis, Z-R; 1R, cis, Z-R and 1S, cis, Z-S). Lambda-cyhalothrin is formed from the enantiomer pair (1R, cis, Z-S; 1S, cis, Z-R). Gamma-cyhalothrin has just one isomer (1R, cis, Z-S) which provides almost all the biological activity among the 4 stereoisomers of cyhalothrin. The ADI was 0.02 mg/kg bw/day for cyhalothrin and an ADI of 0.001 mg/kg bw/day for lambda-cyhalothrin.

Cyhalothrin and lambda-cyhalothrin are listed in Schedule 7 of the SUSDP. There are cut-offs to Schedules 6 and 5 for specific formulations.

DISCUSSION

[Paragraphs deleted]

A member noted that the primary entry proposed for gamma-cyhalothrin was in Schedule 7, and the product containing 15% gamma-cyhalothrin was proposed for inclusion in Schedule 5. Whilst the member concurred that the primary entry should be in Schedule

7, it queried the appropriateness of including the product in Schedule 5, given that the cut-off for lambda-cyhalothrin in this Schedule was 1% for aqueous preparations and 2.5% for microencapsulated aqueous preparations. Furthermore, the member argued that in contrast to lambda-cyhalothrin which is formed from the enantiomer pair (1R,cis,Z-S;1S,cis,Z-R), gamma-cyhalothrin has only one isomer (1R,cis,Z-S), which provides all the biological activity among the 4 stereoisomers of cyhalothrin. On these grounds, it was highlighted that the cut-off from Schedule 7 for gamma-cyhalothrin should reflect this relationship and be less than that specified for lambda-cyhalothrin.

The Committee recalled that the approach taken to date was to accommodate formulated products for agricultural use in lower schedules where appropriate, and that the cut-offs were based on the toxicity profiles of product formulations rather than from extrapolated toxicity values of pure substances. This policy was made on the basis that products were likely to be formulated using different types of solvents and ingredients such that the resulting toxicity profiles were expected to vary. The Committee noted that the type of solvent(s) contained in a formulation, e.g. aqueous vs. organic, etc., and the product presentation, e.g. microencapsulated, significantly influenced the final toxicity profile of a product. Therefore, it was considered an appropriate approach to limit the Schedule entries to apply only to those products considered for scheduling and provide the Committee the opportunity to review the safety of new products/formulations on the market for registration, and consider them for scheduling where appropriate.

DECISION 2003/38 - 9

The Committee agreed that based on the available toxicological data it was appropriate to include gamma-cyhalothrin in Schedule 7 of the SUSDP and include a cut-off to Schedule 5 for aqueous preparations containing 15% or less of microencapsulated gamma-cyhalothrin.

Schedule 7 – New entry

GAMMA-CYHALOTHRIN **except** when included in Schedule 5.

Schedule 5 – New entry

GAMMA-CYHALOTHRIN in aqueous preparations containing 15 per cent or less of microencapsulated gamma-cyhalothrin.

6.3 1-METHYLCYCLOPROPENE

PURPOSE

The Committee considered the scheduling of the new active constituent, 1-methylcyclopropene.

BACKGROUND

XXXXXXXXX submitted toxicological data in support of a new active constituent approval for 1- methylcyclopropene (1-MCP), and for the registration of a new product called XXXXXXXXX. 1-MCP had not been previously considered for scheduling by the NDPSC.

XXXXXXXXX contained 33 g/kg of 1-MCP (active ingredient), 714 g/kg of alpha-cyclodextrin (absorbent/carrier), 213 g/kg of dextrose (carrier, inert) and 40 g/kg of water (solvent). XXXXXXXXX was formulated [deleted]. 1-MCP is a gaseous irreversible inhibitor of ethylene action at the preclimacteric or ripening stages in fruit. Ethylene is the normal physiological plant hormone responsible for fruit ripening, growth inhibition, leaf abscission, and ageing. The treatment was designed to maintain quality and improve the storage potential in a wide range of fruit and vegetables.

DISCUSSION

[Paragraphs deleted]

Whilst the Committee agreed that the toxicological profile of 1- MCP gas for use as a plant growth regulator may be appropriate for exemption from the requirements of scheduling, members however raised the following issues:

- lack of technical information on the nature of the ingredients contained in the product including the XXXXXXXXXX, and that the absence of this information did not allow the Committee to determine whether scheduling was warranted or that it was appropriate to list such ingredients separately in Appendix B of the SUSDP; and
- [Paragraph deleted]

The need to specify the proposed use in the Appendix B entry for 1- MCP was acknowledged, to allow the Committee an opportunity to consider future uses of this chemical.

DECISION 2003/38 - 10

The Committee agreed to exempt 1-methylcyclopropene from scheduling requirements, based on its low toxicity profile in agricultural use as plant growth regulator and include it in Appendix B of the SUSDP. Furthermore, the Committee asked that further information (as outlined above) be sought to allow consideration of scheduling of other substances contained in the product including XXXXXXXXXX.

Appendix B, Part 3 – New entry

1-METHYLCYCLOPROPENE…….June 2003……..a…….1.6

6.4 METARHIZIUM ANISOPLIAE XXXXXXXXX

PURPOSE

The Committee considered the scheduling of *Metarhizium anisopliae* XXXXXXXXX.

BACKGROUND

XXXXXXXXX applied for the registration of two new products, XXXXXXXXX and XXXXXXXXX (both are suspension concentrate formulations), which respectively contained 75 g/L and 300 g/L of conidia of the XXXXXXXXXX of *Metarhizium anisopliae* XXXXXXXXXX. The products were proposed for use in biocontrol of locust and grasshopper pests. XXXXXXXXX was to be sold in a 14-litre container. [Deleted].

Metarhizium is a commonly occurring fungus, found in the soil and often associated with dead insects. *Metarhizium anisopliae* was effective against a wide range of Coleoptera and Lepidoptera species. [Deleted]

Metarhizium anisopliae was exempt from active constituent approval and *Metarhizium anisopliae* as biological control agent is listed in Appendix B of the SUSDP, on the basis that its use pattern restricts the hazard. Registration approval was granted for several products containing *Metarhizium anisopliae*, such as XXXXXXXXX, XXXXXXXXX and XXXXXXXXX, for use in the control of a range of pests including canegrubs, termites and locusts.

DISCUSSION

[Paragraphs deleted]

The issue was raised in regard to the potential for *Metarhizium anisopliae* to cause respiratory sensitivity in immuno-compromised patients. However, on the basis of the evidence available, the Committee was of the view that this risk was not significant.

DECISION 2003/38 - 11

The Committee agreed to exempt *Metarhizium anisopliae* isolate for agricultural use as an insecticide from the requirements of scheduling based on its low toxicity profile and include a separate entry for *Metarhizium anisopliae* for this use.

Appendix B, Part 2 - New entry

1.10 Biological control agent

Appendix B, Part 3 - New entry

Metarhizium anisopliae……..June 2003…….a……..1.10

6.5 MOXIDECTIN

PURPOSE

The Committee considered the proposal to reschedule a pour-on preparation containing 0.5 % or less of moxidectin to be applied externally on the back of cattle or deer to Schedule 5 of the SUSDP.

BACKGROUND

Moxidectin is an endectocide (endoparasiticide and extoparasiticide), an analogue of the antibiotic F28249-α, and structurally related to the macrolides, ivermectin and abamectin.

XXXXXXXXX submitted data in support of an application to reschedule XXXXXXXXX containing 0.5% of moxidectin from Schedule 6 to Schedule 5. The product was used for the treatment and control of moxidectin sensitive internal and external parasites of cattle, and for the treatment and control of lungworm and gastrointestinal roundworms of red deer. This pour-on formulation was to be applied externally on the back of cattle or deer in a line from the withers to the tail.

The August 1993 NDPSC Meeting agreed to include moxidectin in Schedule 7 of the SUSDP based on similarity in structure, acute toxicity profile and teratogenic effects to abamectin and ivermectin, which were already in Schedule 7. A cut-off was also established to Schedule 6 at the time, for injectable preparations containing 0.1% or less of moxidectin for cattle and oral drench for sheep containing 0.2% or less of moxidectin.

The primary entry for moxidectin remained in Schedule 7 to this time, with cut-offs to Schedules 6, 5 and 4. The Schedule 6 entry includes preparations for external use in animals containing up to 2.5% moxidectin presented in single dose tubes for the treatment of cats and dogs, and other preparations containing up to 2% moxidectin. The Schedule 5 entry includes preparations for internal use in animals in either divided preparations for dogs containing up 250 micrograms or less of moxidectin per dosage unit in a pack containing 6 or less dosage units, or, in other preparations containing 2% or less of moxidectin. Moxidectin is also listed in Schedule 4 for preparations for injection containing 10 percent or less of moxidectin.

DISCUSSION

[Paragraphs deleted]

The APVMA advised that the following Schedule 6 external use products registered based on moxidectin content would be affected should a generic 2% cut-off in Schedule 5 be adopted:

- 4 dog products containing 25g/L (2.5%) moxidectin and 100g/L imidacloprid; and
- 2 cat products containing 10g/L moxidectin (1%) and 100g/L imidacloprid.

A member noted that moxidectin and ivermectin had comparable toxicity profiles and that the inclusion of a concentration limit of 2% moxidectin for external use in the Schedule 5 entry would be consistent with ivermectin. In addition, it was also pointed out that preparations for internal use containing 2% or less moxidectin were already included in Schedule 5, and that from an animal health perspective, there were no additional toxicity issues expected from external application of preparations containing up to 2% of moxidectin. On this basis, this member stated that consideration could be given to the inclusion of preparations for external use for the treatment of animals containing 2% or less of moxidectin in Schedule 5 of the SUSDP.

Whilst members recognised that there may be grounds for inclusion of external use preparations containing 2% or less of moxidectin for the treatment of animals such as cattle, sheep or deer in Schedule 5, members did not support the same approach to be taken for external use preparations for the treatment of companion animals or pets such as cats and dogs. It was highlighted that there was a need to retain such products in Schedule 6, on the grounds of high potential for toxicity from physical contact with animals treated with moxidectin, particularly in children. It was also noted that there were no products registered for external use for the treatment of companion animals or pets containing 0.5% or less of moxidectin therefore, it was agreed that a 0.5% limit be specified in the proposed Schedule 5 entry. This was expected to have no regulatory impact on existing products.

DECISION 2003/38 - 12

The Committee agreed to include external use preparations for the treatment of non-companion animals containing 0.5% or less of moxidectin in Schedule 5 of the SUSDP. This decision was based on the evidence of low acute toxicity and in addition, the use pattern of such preparations should limit the potential for exposure direct to the public.

Schedule 5 – Amendment

MOXIDECTIN - Amend entry to read:

MOXIDECTIN

(a) in preparations for external use for the treatment of non-companion animals containing 0.5 per cent or less of moxidectin; or

(b) for internal use for the treatment of animals:

(i) in divided preparations for dogs, containing 250 micrograms or less of moxidectin per dosage unit in a pack containing 6 or less dosage units; or

(ii) in other preparations containing 2 per cent or less of moxidectin.

Schedule 6 – Amendment

MOXIDECTIN - Amend entry to read:

MOXIDECTIN for external use:

(a) in preparations containing 2.5 per cent or less of moxidectin when packed in single dose tubes for the treatment of cats and dogs; or

(b) in preparations containing 2 per cent or less of moxidectin for the treatment of animals.

except when included in Schedule 5.

6.6 BACILLUS THURINGIENSES

PURPOSE

The Committee considered the scheduling of *Bacillus thuringiensis* XXXXXXXXXX.

BACKGROUND

XXXXXXXXX submitted a number of toxicology studies in support of their application for approval of a new active constituent, *Bacillus thuringiensis* XXXXXXXXXX. Registration of a product was not sought at the time, although the applicant indicated that the active constituent was to be used for treatment of sheep to control blowfly strike and lice.

Bacillus thuringiensis is a biological insecticide. Subspecies *kurstaki, aizawai* and *tenebrionis* were used to control various insect pests in plants. Subspecies *israelensis* was used to control mosquitoes and various species of blackflies. The delta endotoxin of *B. thuringiensis* encapsulated in killed *Pseudomonas fluorescens* was listed in Schedule 5 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Strains of *Bacillus thuringiensis* XXXXXXXXXX are common in the fleece of healthy sheep.

Bacillus thuringiensis for use in the control of mosquitoes was listed in Appendix B of the SUSDP based on its low toxicity.

DISCUSSION

[Paragraphs deleted]

A member advised that *Bacillus thuringiensis* was being used in New Zealand as an active ingredient in biological insecticides and that the toxicities seen with end products containing these organisms were mainly attributed to other ingredients present in the formulation, rather than the active itself. The Committee noted that the irritancy potential of end-use formulations would be addressed at registration by appropriate safety directions on the product label.

DECISION 2003/38 - 13

The Committee agreed to exempt *Bacillus thuringiensis* XXXXXXXXXX for use as an ectoparasiticide from the requirements of scheduling based on its low toxicity profile. The Committee also agreed to include a separate entry for *Bacillus thuringiensis* for the use as an ectoparasiticide in Appendix B of the SUSDP.

Appendix B, Part 2 – New entry

2.10 Ectoparasiticide

Appendix B, Part 3 – Amendment

BACILLUS THURINGIENSIS (excluding endotoxin)…. May 1992…….a…….5.1
June 2003…….…a…….2.10

6.7 DIMETHENAMID

PURPOSE

The Committee considered the scheduling of a new active constituent, dimethenamid-P.

BACKGROUND

XXXXXXXXX submitted data to support the approval of a new active constituent, dimethenamid-P, and registration of XXXXXXXXX, an emulsifiable concentrate formulation containing 720 g/L dimethenamid-P.

Dimethenamid belongs to the chloroacetamide chemical group, and is a residual herbicide for the control of annual grasses and broadleaf weeds. The chemical was originally produced as a "racemic" (50/50) mixture of stereoisomers. [Deleted].

No herbicide belonging to the chloroacetamide chemical group had been scheduled in Australia.

DISCUSSION

[Paragraphs deleted]

DECISION 2003/38 - 14

The Committee agreed to include dimethenamid-P in Schedule 6 of the SUSDP, on the basis of it toxicological profile.

Schedule 6 – New entry

DIMETHENAMID-P.

6.8 BOSCALID

PURPOSE

The Committee considered the scheduling of a new active constituent, boscalid.

BACKGROUND

XXXXXXXXX submitted data in support of active constituent approval for boscalid (2-chloro-N-(4"-chlorobiphenyl-2-yl)nicotinamide (IUPAC)), and for the registration of the new product, XXXXXXXXX. The proposed product was a water dispersible granule formulation containing 500 g/kg of boscalid, for use in the control of bunch rot (Botrytis cinerea) in grapevines.

Boscalid is a benzanilide (oxathiin) fungicide (eg. flutolanil, carboxin and oxycarboxin), and inhibits spore germination, germ tube elongation, mycelial growth and sporulation by inhibition of succinate ubiquinone reductase (complex II) in the mitochondrial electron transport chain.

Boscalid had not been previously considered for scheduling by the NDPSC however, related compounds such as flutolanil and carboxin, both for agricultural use, had been listed in Appendix B of the SUSDP on the grounds of low toxicity.

DISCUSSION

[Paragraphs deleted]

DECISION 2003/38 - 15

The Committee agreed to exempt boscalid for agricultural use (a) as fungicide (1.3) from the requirements of scheduling based on its low toxicity profile and list the substance in Appendix B.

Appendix B, Part 3 – New entry

BOSCALID……..…June 2003……..a……1.3

6.9 CINMETHYLIN

PURPOSE

The Committee considered the scheduling of the new active constituent, cinmethylin.

BACKGROUND

XXXXXXXXX submitted data for the approval of the active constituent cinmethylin, a novel 1,4 cineole herbicide. Cinmethylin is a 2-benzyl ether substitute analogue of the monoterpene 1,4-cineole, a derivative of the natural monoterpene 1,8-cineole. Products based on cinmethylin were to be used primarily in wheat, and possibly canola.

DISCUSSION

[Paragraphs deleted]

DECISION 2003/38 - 16

The Committee agreed to include cinmethylin in Schedule 5 of the SUSDP, based on the substance's skin irritancy potential.

Schedule 5 – New entry

CINMETHYLIN.

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

No items were considered

8. ANTIBIOTICS FOR CONSIDERATION FOLLOWING RECOMMENDATIONS OF THE JOINT EXPERT TECHNICAL ADVISORY COMMITTEE ON ANTIBIOTIC RESISTANCE (JETACAR)

8.1 NISIN

PURPOSE

The Committee considered the scheduling of nisin.

BACKGROUND

Nisin is a polypeptide antibiotic produced by *Streptococcus lactis*, a naturally occurring milk bacterium, and is approved as a food additive in Australia and used as a food biopreservative in a wide range of food products including dairy, fermented beverages, dressings and sauces, frozen desserts and high moisture/reduced fat foods. Nisin inhibits many Gram-positive foodborne pathogens, including *Clostridium botulinum* and *Listeria monocytogenes*. In these bacteria, nisin acts on the cytoplasmic membrane of the nisin-sensitive cell by binding, inserting and forming pores. This leads to efflux of intracellular compounds, energy depletion, proton motive force dissipation, and ultimately cell death. Nisin was listed as "Generally Regarded as Safe" (GRAS) in the United States in April 1988, and is also approved as a natural food preservative by more than 40 countries as well as with the Food and Agricultural Organisation of the United Nations and European Union.

The May 1978 Meeting agreed to specifically exclude nisin, which was considered exempt from scheduling at the time, from the generic entry for 'antibiotics' in Schedule 4. The November 1992 Meeting was advised, following an initial review of Appendix B entries by the Secretariat, that nisin was included in the list of Appendix B compounds for which a scheduling rationale could not be established because the minutes from the relevant meeting consideration could not be located. In November 1998, XXXXXXXXXX agreed to adopt the Schedule 4 generic statement for antibiotic substances but did not adopt the exemption for nisin although no reason was stated in the XXXXXXXXXX. Nisin was included in the draft Appendix B list, but removed prior to the February 2003 NDPSC Meeting.

The February 2003 NDPSC Meeting noted the Expert Advisory Group on Antimicrobial Resistance (EAGAR) Secretariat's interim advice that there were no resistance issues associated with nisin as it is in a class that has no human analogues or cross-resistance issues. However, a recent study published under the auspices of the United States Department of Agriculture, Agriculture Research Service reported that the ruminal bacterium, *Streptococcus bovis*, could develop nisin resistance after only a short period of exposure. It was stated that this was due to an alteration in lipoteichoic acids, and this change also caused an increase in ampicillin resistance. The Committee agreed to refer the US published paper to the EAGAR for consideration and to gazette the consideration of nisin for the June 2003 meeting.

DISCUSSION

The Committee noted the EAGAR's assessment which recommended that the use of nisin as an approved food additive according to the ANZ Food Standards Code be continued and recommended that nisin not be included in Schedule 4 of the SUSDP. The rationale for this recommendation is as follows:

- Nisin is an approved food additive (number 234) and, according to the ANZ Food Standards Code, it may be used in dairy products, oil emulsions, tomato products,

fruit and vegetable preparations, flour products, liquid eggs, beer, dips, sauces and toppings.

- Although the potential value of nisin in human medicine has been suggested by *in vitro* studies where it demonstrated synergy with other compounds that inhibit cell wall synthesis, nisin has never been used therapeutically in human medicine.

- Nisin does not confer cross-resistance to other agents in the same class.

The Committee noted that there were no products containing nisin listed on the ARTG or on PUBCRIS.

DECISION 2003/38 - 17

The Committee agreed that the unscheduled status of nisin for use as a food additive remains appropriate and supported the inclusion of nisin in Appendix B of the SUSDP on the basis that it is not used in human or veterinary medicine and it does not confer cross-resistance to other agents in the same class.

Appendix B – Part 3 – New Entry

NISIN ……..…June 2003……..a……3.2

8.2 APRAMYCIN

PURPOSE

The Committee considered the scheduling of apramycin.

BACKGROUND

Apramycin is an aminoglycoside antibiotic used as the sulfate in veterinary practice for the treatment of susceptible infections. Apramycin was first considered by the NDPSC in August 1986 and concerns over its similarities to other human antibiotics and possible bacterial resistance to these substances were noted in the meeting minutes. The inclusion of apramycin in Schedule 4 of the SUSDP was foreshadowed pending receipt and evaluation of pharmacokinetic data relating to absorption via the oral route from the sponsor and it was recommended to seek the view of the antibiotics committee with regards to the implication of cross-resistance. Due to an oversight, apramycin was not separately included in Schedule 4 of the SUSDP.

XXXXXXXXX made a submission to the NDPSC for review by the Expert Advisory Group on Antimicrobial Resistance (EAGAR) in which they advised that current practices require administration of apramycin under Schedule 4 status. XXXXXXXXX also stated that the overall amount of apramycin used in swine is minimal in comparison to other therapeutic options and that continued improvements in quality assurance,

slaughter and processing and cooking practices will result in additional safeguards that minimise salmonella contamination.

DISCUSSION

The Committee noted the assessment from the EAGAR which recommended that all uses of apramycin be included in Schedule 4 of the SUSDP as it poses an unacceptable resistance risk of promoting cross-resistance to aminoglycosides of human importance when available outside Schedule 4. Although apramycin is not used in human medicine, resistance to apramycin has been demonstrated to transfer from animal bacteria to human bacteria and can cause cross-resistance to gentamycin (rated as low human importance) and netilmicin (rated as high human importance).

The Committee noted that there were two apramycin products currently registered with the APVMA (XXXXXXXXX and XXXXXXXXX). Since they are both labelled as "Prescription Animal Remedy", the Committee determined that there would be no regulatory impact by placing apramycin for all uses in Schedule 4 of the SUSDP.

DECISION 2003/38 - 18

The Committee agreed to include apramycin for all uses in Schedule 4 of the SUSDP on the basis that the use pattern is consistent with Schedule 4 and that resistance to apramycin has been demonstrated to transfer from animal bacteria to human bacteria and can cause cross-resistance to gentamycin (rated as low human importance) and netilmicin (rated as high human importance).

Schedule 4 – New entry

APRAMYCIN.

8.3 CEFADROXIL

Deferred to October 2003 meeting.

8.4 PENETHAMATE HYDRIODID

Deferred to October 2003 meeting.

8.5 THIOSTREPTON

PURPOSE

The Committee considered the scheduling of thiostrepton.

BACKGROUND

Thiostrepton is an antibacterial substance used in topical preparations for veterinary use. XXXXXXXXX markets an ointment containing thiostrepton, called XXXXXXXXX (containing triamcinolone acetonide 1 mg/mL, neomycin sulfate 2.5 mg/mL, thiostrepton 2 500 units/mL and nystatin 100 000 units/mL) for the treatment of most skin and ear infections in dogs and cats, and bovine infectious keratoconjunctivitis of cattle, which is currently labelled as a Schedule 4 product. Thiostrepton is not individually listed in the SUSDP, however is covered by the general antibiotic substances entry in Schedule 4.

DISCUSSION

The Committee noted the submission received from XXXXXXXXX for review by the Expert Advisory Group on Antimicrobial Resistance (EAGAR) stated that they have no objection to the proposed inclusion of thiostrepton in Schedule 4 of the SUSDP.

The Committee considered the EAGAR's scheduling assessment which recommended that all uses of thiostrepton be included in Schedule 4 of the SUSDP. Although the EAGAR human importance rating was low for thiostrepton, the rationale for this recommendation was that the mode of action and mechanism of resistance is similar to bacitracin, which was also recommended to be included in Schedule 4 of the SUSDP for all uses.

The Committee noted that there is only one thiostrepton product currently registered with the Australian Pesticides and Veterinary Medicines Authority (APVMA) XXXXXXXXX which is currently labelled as "Prescription Animal Remedy", therefore there would be no regulatory impact by placing thiostrepton for all uses in Schedule 4 of the SUSDP.

DECISION 2003/38 - 19

The Committee agreed to include thiostrepton for all uses in Schedule 4 of the SUSDP on the basis that availability as a non-prescription product would raise the likelihood of escalating resistance when used therapeutically in animals and as such, would pose an unacceptable risk of promoting antimicrobial resistance.

Schedule 4 – New entry

THIOSTREPTON.

8.6 PHTHALYLSULFATHIAZOLE

Deferred to October 2003 meeting.

9. OTHER MATTERS FOR CONSIDERATION

No items considered.

10. INITIAL REVIEW AND/OR FORMAL OPINIONS (AG/VET, INDUSTRIAL & DOMESTIC CHEMICALS)

10.1 DIETHYLENE GLYCOL MONOBUTYL ETHER

PURPOSE

The Committee considered a request for clarification regarding the scheduling of diethylene glycol monobutyl ether.

BACKGROUND

Ethylene glycol monoalkyl ethers and their acetates except in preparations containing 5 per cent or less of these substances were initially included in Schedule 6 of the SUSDP at the November 1984 NDPSC meeting, based on toxicological data. Prior to this meeting, ethylene glycol monoalkyl ethers were exempt from the requirements of scheduling.

The May 1992 meeting considered a toxicology review of glycol ethers including diethylene glycol alkyl ethers and their acetates but no consequential changes to the scheduling of this class of chemicals came into effect.

DISCUSSION

XXXXXXXXX sought clarification on whether diethylene glycol monobutyl ether was covered by the class entry for ethylene glycol monoalkyl ethers in the SUSDP. In addition, XXXXXXXXX indicated that they reviewed data in relation to the toxicology of ethylene glycol and diethylene glycol monobutyl ether, which showed that the latter was of low toxicity. However, the data set referred to in the company's correspondence was not submitted to the Committee for consideration.

OUTCOME

The Committee confirmed that diethylene glycol monobutyl ether was included in the Schedule 6 entry for ethylene glycol monoalkyl ethers, based on the provisions set out in Part 1, paragraph 2(c) of the SUSDP, i.e. unless the contrary intention appears, a reference to a substance in a schedule or an appendix to this Standard includes every salt, active principle or derivative of the substance, including esters and ethers, and every salt of such an active principle or derivative. However, the Committee indicated that it was willing to consider a proposal to establish a cut-off from Schedule 6 to lower schedules or to exempt, if such a request was supported by an appropriate submission in accordance with the NDPSC Guidelines for Application and Information Requirements.

11. INFORMATION ITEMS (AG/VET, INDUSTRIAL & DOMESTIC CHEMICALS)

11.1 HYGROMYCIN

PURPOSE

The Committee received the risk assessment of hygromycin from the Expert Advisory Group on Antimicrobial Resistance (EAGAR).

BACKGROUND

Hygromycin B is an aminoglycoside antibiotic that inhibits protein synthesis in bacteria and fungi. It is used as an anthelmintic in veterinary medicine for the treatment of nematode infections.

The EAGAR had not finalised their formal advice for hygromycin before the February 2003 NDPSC Meeting, however provided the Committee with an interim recommendation of S4 for all uses as hygromycin selects for cross-resistance to aminoglycosides of human importance. The Committee agreed to include hygromycin for all uses in Schedule 4 of the SUSDP on the basis of the EAGAR's interim advice and for consistency with the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) Recommendation 6 where the risk of promoting antibiotic resistance as a non-prescription product is unacceptable.

DISCUSSION

The Committee noted the EAGAR's assessment which recommended that all uses of hygromycin be included in Schedule 4 of the SUSDP as it poses an unacceptable resistance risk of promoting cross-resistance to aminoglycosides of human importance when outside Schedule 4. This was consistent with the decision made at the February 2003 NDPSC Meeting.

The Committee also noted that although hygromycin is not used in human medicine, resistance to hygromycin is co-selected with resistance to apramycin (also not used in human medicine). This resistance has been demonstrated to transfer from animal bacteria to human bacteria and can cause cross-resistance to gentamycin (rated as low human importance) and netilmicin (rated as high human importance).

OUTCOME

The Committee noted the EAGAR risk assessment of hygromycin.

PHARMACEUTICALS

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

12.1 IRON COMPOUNDS

PURPOSE

The Committee considered the pack size limit included in the Schedule 2 entry for iron compounds.

BACKGROUND

The February 2002 NDPSC Meeting amended the Schedule 2 entry in the SUSDP for iron compounds to raise the pack size limit from 600 mg to 750 mg. The October 2002 NDPSC Meeting considered a request for clarification relating to the Schedule 2 entry for iron compounds, specifically in relation to iron oxides when present as an excipient. The Committee confirmed that the cut-off for exemption for iron oxides in Schedule 2 of the SUSDP applied to preparations containing less than 10 mg of total iron oxides or 1% of total iron oxides (not the equivalent iron content). However, the Committee was of the view that the existing Schedule 2 entry for iron compounds did not clearly reflect this intent and agreed that the matter be referred back to the February 2003 Meeting to amend the entry for consistency with the intent of the Committee.

The February 2003 NDPSC Meeting agreed to amend the Schedule 2 entry for iron compounds to exempt 10 mg or less in divided preparations and 1% or less in undivided preparations of total iron oxides when present as an excipient, however the pack size was inadvertently change from 750 mg or less to 600 mg or less. The item was referred back to the June 2003 Meeting following post-meeting comment.

DISCUSSION

The Committee noted an email received from XXXXXXXXX of the XXXXXXXXX reporting an editorial error in the Schedule 2 entry for iron compounds that was published as part of the outcomes of the February 2003 NDPSC Meeting. The Committee also noted the correspondence received from XXXXXXXXX on the same issue.

The Committee acknowledged that the pack size limit was inadvertently changed when the amendment was made concerning the exclusion for iron oxides used as excipients.

DECISION 2003/38 – 20, Erratum: Correction of Decision 2003/37 - 25

The Committee agreed to restore the pack size to 750 mg through an editorial amendment to the original decision arising from the February NDPSC Meeting, with the effective date remaining 1 September 2003.

Schedule 2 – Amendment

IRON COMPOUNDS – correct to read:

IRON COMPOUNDS (excluding iron oxides when present as an excipient, in divided preparations containing 10 mg or less of total iron oxides per dosage unit or in undivided preparations containing 1 per cent or less of total iron oxides) for human internal use **except**:

(a) when included in Schedule 4; or

(b) when labelled with a recommended daily dose of 24 mg or less of iron:

(i) in undivided preparations supplied in packs each containing 750 mg or less of iron; or

(ii) in divided preparations:

(A) containing more than 5 mg of iron per dosage unit in packs each containing 750 mg or less of iron; or

(B) containing 5 mg or less of iron per dosage unit.

13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

13.1 MELIA AZEDARACH

PURPOSE

The Committee considered the foreshadowed entry of *Melia azedarach* in Appendix C of the SUSDP.

BACKGROUND

Melia azedarach, also called Chinaberry or White Cedar (also known in Australia as "white mahogany"), is a member of the *Meliaceae* family and grows in subtropical areas in Asia, Australia, Hawaii, Africa, South America and parts of the southern United States.

The fruit and the bark were considered poisonous and there was great variability in the symptoms seen due to genetic variation of the plant. The ingestion of as few as 6-8 berries had been fatal in some geographic locations but in other areas the fruits may be eaten without harm. The ripe fruit was thought to be more toxic than the unripe fruit, which was more toxic than other parts of the plant (POISINDEX). Parts of the plant which were used for medicinal purposes were the bark, fruits, root bark, leaves and flowers. Uses for *Melia azedarach* included the following: stimulant, insecticide, anthelmintic, antiviral, anticancer agent, astringent, purgative, treatment for leprosy and various types of skin diseases, treatment for headlice, liver tonic, antiseptic, treatment for nausea, vomiting, loss of appetite, for general debility, maintenance of a healthy digestive system, carbohydrate metaboliser and treatment of menstrual pain.

The June 2002 NDPSC meeting agreed to foreshadow the inclusion of *Melia azedarach* or its extracts or its derivatives in Appendix C of the SUSDP, on public health and safety grounds. Whilst the Committee was of the view that there was a need to restrict the use of *Melia azedarach* on safety grounds, it recommended that additional information be sought to help resolve the following issues:

- Is there a mechanism for ensuring that only the non-toxic variety is used in products, given that the toxic variety has been found to be botanically indistinguishable from the non-toxic variety?
- Is it safe to establish a concentration cut-off to accommodate existing products?
- What are the long-term effects of *Melia azedarach* in humans and animals given that its limonoids have been found to be highly cytotoxic?
- What is the appropriate approach for veterinary products, given that *Melia azedarach* has also been established to be highly toxic in animals?

The October 2002 meeting considered the foreshadowed entry of *Melia azedarach* in Appendix C of the SUSDP but agreed to defer the matter to the June 2003 meeting to allow affected stakeholders a reasonable opportunity to provide relevant data to the Committee.

DISCUSSION

The Committee noted that XXXXXXXXX raised the following points for consideration:

- The use of Liquid Chromatography/Mass Spectrometry (LCMS) for the identification of *Melia azedarach* from another similar species was successfully conducted. The use of specific mass spectra to differentiate various species should provide a mechanism for ensuring that only the non-toxic variety of *Melia azedarach* or toosendanin was used in products.
- The CRC Handbook of Ayurvedic Medicinal Plants provided doses for various finished forms of *Melia azedarach* including powder root bark and powder fruits. According to the *Pharmacology and Applications of Chinese Materia Medica*, the bark and root bark of *Melia azedarach or M. toosendan* contained mainly toosendanin

($C_{30}H_{38}O_{11}$), where the LD_{50} was 2194 mg/kg PO in mice. Severe reactions could appear if the toosendanin dose was over 0.8 mg in adults which could include neuritis, arrhythmia, hypotension, and dyspnoea and therefore should be used with caution, or avoided in patients with severe heart disease, gastric ulcer, anaemia and in those with weak constitutions. It was contraindicated in patients with liver diseases. Toosendanin was used mainly as an anthelmintic at doses of up to 250 mg per dose for adults and was not recommended for continuous use.

XXXXXXXXX provided a late submission on behalf of XXXXXXXXX in relation to the proposed inclusion of *Melia azedarach* in Appendix C of the SUSDP. The following points were raised for consideration:

- Melia leaf had a long history of safe use in Asia. No reports of human toxicity of Melia leaf could be found in the general herbal or ethnographic literature. Certified herbalists in Australia used leaf extracts of *Melia azedarach* variety *Australasica* (20% w/v) clinically for many years with no reports of adverse effects.
- Cytotoxic assays using crude fresh leaves of *Melia azedarach* were found to be toxic at low dilutions (less than or equal to 1:10), although the fractions which exhibited antiviral activity were devoid of toxicity.
- The alcoholic and aqueous extracts of flowers and berries were non-toxic in rats and mice to a dose of 1500 mg/kg. However, some toxic symptoms were observed within this dosage range, including mild central nervous system (CNS) sedation. Intravenous administration led to more severe symptoms at sub-lethal doses. These included vasodilation followed by vasoconstriction, respiratory depression, pupilliary constriction, hyperirritability, tachycardia, dried mouth and micturition. In doses where mortality was observed, it was noted that death occurred due to cessation of respiration (Zakir-ur-Rahman et al. 1991).
- The leaves, bark and flowers had been shown to be toxic, but most cases occurred after eating ripe fruits. Toxic principles in fruit had been identified as meliatoxins and it appeared that the toxin or toxins were similar in the different forms of the trees growing in Australia, Africa, Asia or the Americas (Oelrichs et al. 1884).
- Entry of the species in Appendix C would cease further research on one of the most promising antiviral agents currently available.
- The following scheduling options were proposed:

  - XXXXXXXXX proposed that preparations based on 'leaf only' be exempted from scheduling.

  - A concentration cut-off of 10-20% dried herb equivalent could be established as well as a maximum dosage limit.

  - Consideration should be given to establishing a 'Practitioner Only Listed Medicine' category, restricting usage to a group of professionally accredited practitioners.

The Committee noted that the Office of Complementary Medicines (OCM) did not support the inclusion of *Melia azedarach* and its extracts and derivatives in Appendix C of the SUSDP. The OCM raised the following points for consideration:

- Simple preparations of *Melia azedarach* (and the closely related *Melia toosendan*) had been used in traditional medicines systems such as traditional Chinese medicine (TCM) and Ayurvedic medicines for a considerable time (many decades at the least).
- Recommended dosages within these systems of medicine ranged from 4.5-15g (or up to 60g when used alone) of the dried stem or root bark, and 3-9g of the dried fruit. However, both Chinese and Indian systems of medicine recognised the potential toxicity of the preparations at high doses and indicated that such preparations should not be taken long-term.
- Most cases of acute toxicity appeared to occur when fresh fruit was ingested from on or around the tree. There appeared to be considerable variability in the toxic symptoms experienced. There was one report of a child dying after ingestion of 6-8 berries (of an African variety of the tree), and many cases of livestock toxicity following ingestion of the fallen fruit. Paradoxically, in some areas, children and animals commonly ingested the fruit with no apparent untoward effects.
- It appeared that different chemotypes (plants within the same species with different chemical profiles) of *Melia azedarach* may be responsible for the variability of toxicity reported. Unfortunately, chemotypes may be botanically indistinguishable.
- Some reports indicated that a group of tetranortriterpinoids of the limonoid class (found in the fruits of *Melia azedarach Var. Australasica*), termed meliatoxins A1, A2, B1 and B2 may be responsible for the acute nervous symptoms and potential death.
- It was likely that some forms of restriction were warranted for some preparations and/or plant parts of *Melia azedarach*, such as label warnings or potentially registration of therapeutic goods containing particular preparations or plant parts of this herb.
- There were 17 products listed in the Australian Register of Therapeutic Goods (ARTG) which included *Melia azedarach* as an ingredient. Five of these products contained *Melia azedarach* as a dried powder of the fruit or seed, ranging from 8.5mg –1g/g. five products contain a decoction (boiled water extraction) of the stem bark or fruit (dry equivalents ranging from 142 – 670mg). Four products contained dried aqueous extracts of the fruit (dry equivalents 105-340mg/tablet), and three products contain ethanol:water extracts (~50:50) of the leaf (dry equivalents 37.5mg/ml, 1g/ml, and 1.96g/tablet). It should be noted that tetranortriterpinoids were unlikely to be extracted in aqueous extracts of the plant.
- Most products carried claims for digestion or as a 'liver tonic', 5 for cystitis or menstrual symptoms, 1 for dry or inflamed skin, and 1 topical product made claims for treating head lice. NB: Where the fruit was entered as a plant part, it was possible that what was being used would qualify as *Melia toosendan* in the *Pharmacopoeia of*

the People's Republic of China. If this was the case, most potential doses of the herb(s) included in Listed medicines appeared well below that recommended in the Chinese Pharmacopoeia and the *Chinese Herbal Medicine Materia Medica*.

- The OCM proposed that a more complete safety review of *Melia azedarach* be undertaken, with input and advice from the Complementary Medicines Evaluation Committee (CMEC). This should allow a more in-depth analysis of papers reporting on the potential toxic compounds found in this plant. It was suggested that a full report on the safety of *Melia azedarach* could be completed and submitted to the CMEC by late this year.

The OCM also advised that there was no formal definition of 'practitioner' or 'practitioner only' in the therapeutic goods legislation. However, under the provisions of Therapeutic Goods Order No. 69 *General requirements for labels for medicines* (TGO 69) (the standard which dealt with the labelling of therapeutic goods) there were exemptions that applied to products labelled with the words "For Practitioner Dispensing Only".

OUTCOME

The Committee noted that the data available at the meeting was not sufficient to resolve the issues raised in regard to the toxicity associated with the *Melia azedarach* plant. The Committee agreed to defer further consideration of the foreshadowed inclusion of *Melia azedarach* in Appendix C of the SUSDP to the February 2004 to allow the OCM sufficient time to complete the safety review on *Melia azedarach.*

13.2 MOMETASONE - PAEDIATRIC USE

PURPOSE

The Committee considered an application seeking to include mometasone for the short-term prophylaxis and treatment of allergic rhinitis (AR) in children aged between three and eleven years in Schedule 3 of the SUSDP.

BACKGROUND

Mometasone has been approved by Australian Drug Evaluation Committee (ADEC) for the treatment or prophylaxis of allergic rhinitis in children aged 3-11 years and is currently in schedule 4 of the SUSDP.

The October 2002 NDPSC meeting considered the proposal to include mometasone in Schedule 3 for the short-term prophylaxis and treatment of AR in adults and children aged 3 years and over. The Committee agreed to extend the indication of mometasone in Schedule 3 to include the short-term prophylaxis and treatment of AR in adults and children aged twelve years and over. Further consideration of the proposal to extend the S3 indication to include children, aged 3 years and over, was deferred so the Committee could seek further advice on the suitability of use of this agent without the intervention of a medically qualified professional.

To resolve the issues of whether there was a need for initial diagnosis or assessment by a medical professional before and during administration of intranasal mometasone in children less than 12 years of age and whether there was potential for growth suppression with long-term use of intranasal mometasone, the NDPSC Secretariat sought advice from ADEC, Medicines Evaluation Committee (MEC), XXXXXXXXX and XXXXXXXXX.

DISCUSSION

The Committee considered the responses from ADEC, MEC, XXXXXXXXX and XXXXXXXXX.

The ADEC considered this matter at the 227 meeting held on 2- 4 April 2003. The ADEC agreed to recommend to the NDPSC that intranasal corticosteroid treatment of allergic rhinitis in children aged 3-11 years should remain in Schedule 4 and made the following recommendations:

- There is a need for an accurate initial diagnosis, particularly in pre-school and primary school children for the reason that nasal symptoms in these age groups are easily confused- infective, non-allergic and allergic; that perennial rhinitis is relatively more common in children than seasonal rhinitis; nasal steroids in children are almost never for short term prophylaxis of seasonal rhinitis, but are used over a much longer time period for treatment of perennial rhinitis. Initial assessment should include examination for nasal obstruction and associated atopic diseases.
- There is no data that would support the potential for growth suppression.
- The ADEC concluded that there is a need for on-going management of treatment by a medical practitioner as:-

  – *Perennial allergic rhinitis is relatively more common in young children, compared with seasonal rhinitis.*

  – *Treatment with intranasal steroids is likely to be required for longer than six months.*

  – *Associated conditions frequently occur, such as asthma and the child needs to be assessed medically as part of routine follow-up.*

  – *Complications of perennial allergic rhinitis require medical intervention.*

- Other treatment modalities, such as allergen avoidance or additional medication may be required and it would be difficult for pharmacists to select those patients who would benefit from other therapies.

The ADEC agreed that there remains a great deal of confusion about the relative incidence of seasonal and perennial rhinitis in young children, about the different approaches to and indicators for, particular treatments and the duration of therapy

required. Overall ADEC had no concerns regarding the safety of intranasal corticosteroids, but did have reservation regarding adequacy of initial diagnosis and assessment.

The MEC considered the proposal at its meeting of 3 April 2003 and recommended that the Schedule 3 entry for mometasone should not be extended to also include children aged 3 to 11 years on the basis that children under 12 years should always be assessed by a medical practitioner before giving nasal corticosteroids.

The XXXXXXXXX considered the proposal at their Council meeting on 6 March 2003. XXXXXXXXX's opinion was that in children aged 3 to 11 years:

- There is a need for initial diagnosis and assessment by a medical professional before administration of intranasal mometasone.
- There is potential for hypothalamic/pituitary/adrenal axis and growth suppression from long term use of intranasal mometasone.
- There is a need for on-going management of treatment by medical practitioner.

XXXXXXXXX recommended that no extension of the Schedule 3 entry is made for children less than 12 years.

The XXXXXXXXX advised:

- There is a need for an accurate initial diagnosis particularly in primary and pre school age children.
- The available evidence indicates that this has not been a significant problem associated with the use of topical intranasal corticosteroids. There is no evidence that topical mometasone is associated with systemic effects on growth.
- In relation to on-going management, treatment needs to be initiated and supervised by a medical practitioner.

The Committee noted the pre-meeting comment from XXXXXXXXX which highlighted that controlled trials have shown that intranasal corticosteroid may cause a reduction in growth velocity in children though the long-term effects in growth velocity and final adult height is unknown. XXXXXXXXX believed that mometasone should be available for paediatric use with consultation to a doctor or pharmacist in order to receive the appropriate dose to minimise the systemic effects of intranasal corticosteroids in children.

Members also took into account the previous evaluation report for the October 2002 meeting which concluded that mometasone is a topical glucocorticoid with local anti-inflammatory properties with very low systemic bioavailability when used as an intranasal spray for allergic rhinitis and is safe and effective in children when given as 100μg/day in allergic rhinitis. The clinical trial data set revealed no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression. There was also no evidence of HPA axis suppression after long-term (12 months) treatment with approved paediatric doses of mometasone (100μg/day) in a number of clinical trials and published literature.

Furthermore, there was no evidence of growth retardation in terms of rate of lower leg growth in short-term (2 week use) with 100 or 200µg/day nor any evidence of growth retardation in a 12 month multicentre, double-blind, placebo-controlled study with 100µg/day. The evaluator concluded that there are no substantially different local adverse effects to those seen with placebo or active comparators and that there was little or no evidence of use or misuse in the paediatric population. However, the degree of exposure in children since marketing was not clearly discernible from the point of view of the periodic safety update report provided.

The Committee noted XXXXXXXXX had supplied international line-listings detailing the adverse events reported in paediatric patients following treatment with intranasal mometasone furoate. During the period 19 February to 18 September 2001, XXXXXXXXX units were sold worldwide with 656 adverse events reported. Since the first international launch there have been a total of 75 adverse events to intranasal mometasone furoate reported in paediatric group. Australian sale data for 2001 indicated approximately XXXXXXXXX of scripts for intranasal mometasone were for patients under 12 years.

The Committee noted the Evaluator had subsequently reviewed the line listings provided from XXXXXXXXX, and the responses received from MEC, XXXXXXXXX and XXXXXXXXX. It was concluded that although this agent in the paediatric age group is acceptably safe according to global adverse event reports, there is concern, as expressed by relevant professional groups, that this agent in the younger age group needs to be aligned with an initial medical diagnosis and monitoring. The Evaluator recommended the Schedule 4 listing be retained.

A member advised that there is evidence emerging, in the last two years, of adverse effects in paediatrics using fluticasone, which has a similar pharmacokinetic profile to mometasone. This was not expected theoretically. The member expressed a general concern of the use of corticosteroids in paediatrics.

The Committee was of the view that it would be prudent to be cautious with regard to the availability of intranasal corticosteroids for treatment of allergic rhinitis in children under 12 years.

OUTCOME

The Committee agreed that intranasal mometasone for the prophylaxis and treatment of allergic rhinitis (AR) in children aged between three and eleven years be retained in Schedule 4, as there is a need for initial diagnosis and ongoing management of treatment by a medical professional.

13.3 AZADIRACHTA INDICA (NEEM)

PURPOSE

The Committee considered the requirement of a Child-Resistant Closure (CRC) on all liquid preparations of *Azadirachta indica* (neem) when included in Schedule 6 and packed in a container with a nominal capacity or 2 litres of less.

BACKGROUND

The scheduling of *Azadirachta indica* (neem) was considered at the October 2002 NDPSC Meeting and the Members stated that they remained concerned over the potential toxicological hazards from oral and dermal exposure to neem and its extracts/derivatives. The evidence reviewed by the Committee included reports of serious poisonings in children and embryotoxic, abortifacient and anti-androgenic effects in laboratory animals. On these grounds, the Committee agreed that the availability and presentation of neem products for sale to the public warranted restrictions in order to protect public health and safety. Hence, the Committee recommended that preparations containing neem or its extracts or its derivatives for human internal use be prohibited in Australia, except those containing "debitterised" neem seed oil. The Committee also agreed that products other than those for human internal use may remain available for sale to the public provided they are appropriately labelled and packaged.

Post-meeting submissions were considered at the February 2003 NDPSC meeting, at which the Committee confirmed the October 2002 *Azadirachta indica* (neem) decision on the grounds that the toxicity profile including the acute, reproductive and foetal toxicity of the substance warranted scheduling. The Committee also agreed to foreshadow the inclusion of a CRC requirement for Schedule 6 liquid preparations containing 2 litres or less of cold pressed neem seed oil in Part 2 of the SUSDP.

Members noted at the February 2003 NDPSC meeting that the scheduling decision on *Azadirachta indica* (neem) from the October 2002 meeting did not include a requirement for Schedule 5 and 6 *Azadirachta indica* (neem) products to be fitted with a CRC. The Committee agreed that this was inconsistent with the original intent of these entries and that the inclusion of a requirement for a CRC on containers for Schedule 6 *Azadirachta indica* (neem) products in liquid form should be gazetted and formally considered at the June 2003 Meeting. The Committee did not support a requirement for a CRC on Schedule 5 products on the basis that agricultural products included in Schedule 5 were unlikely to be used in the home setting and unlikely to be available in the small volumes that are typical of products for domestic use.

DISCUSSION

The Committee noted the following pre-meeting submissions:

- XXXXXXXXX objected to the proposed CRC requirement on Schedule 6 agricultural neem products. Their submission stated that there was no practical

difference between Schedule 5 and Schedule 6 agricultural neem products ie they are equally unlikely to be used in the home setting and unlikely to be available in small volumes typical of products for domestic use. Therefore, XXXXXXXXX considered that the reasoning used by the Committee to exclude Schedule 5 agricultural neem products from the CRC requirement could also be applied to Schedule 6 agricultural products.

- XXXXXXXXX objected to the proposed CRC requirement on Schedule 6 products on the grounds that he will be unable to comply and therefore be unable to continue marketing his products. XXXXXXXXX originally attempted to comply with the requirements to ensure that his product was exempt from scheduling, however he has been unable to source a suitable CRC for his products. XXXXXXXXX subsequently decided to label and market his products in accordance with the Schedule 6 requirements to avoid the need for a CRC, but will not avoid this requirement if the proposed amendment is made.

The Committee noted that the Schedule 5 entry for neem was created to accommodate a product intended for use as an in furrow application to prevent false wire worm damage to cotton seed at the time of planting. This application appeared to be the only pattern of use for the type of extract specified in the Schedule 5 entry and was unlikely to be used in the home garden setting. However, the Committee acknowledged that the products covered by the Schedule 6 entry may find application in the home garden and a CRC may be appropriate on these products. The Committee noted that this requirement would not be necessary on pack sizes larger than 2 litres, therefore there would be no regulatory impact on larger pack sizes used in agriculture.

A Member presented samples of XXXXXXXXX packaging to the Committee. The packaging consisted of a standard plastic bottle with either a "witches hat" cap or a spray head attached. The witches hat was sealed at the tip which needed to be cut off when the product was first used. The spray head was covered by a clear plastic cap. The Member informed the Committee that both the witches hat and the spray head were needed to facilitate the correct use of the product ie the product is applied to the scalp where the head lice live, and that they controlled the flow of the product during application. This also served to limit the amount that a child could extract from the bottles. If these attachments were removed and replaced by a CRC, the neck of the bottle would allow a greater amount of product to be applied to the scalp, which could result in the product dripping over the face and may lead to greater inadvertant/inappropriate exposure. The Committee acknowledged XXXXXXXXX comments concerning the inability to find suitable CRC's for his products.

A Member noted that a number of other products which contained Schedule 6 substances that are stored in the home such as hair dyes do not currently require a CRC eg toluenediamine, phenylenediamines and hydrogen peroxide. However, the Committee also noted that these products did not present the same level of risk as they were single-use products and were packaged in an outer carton. This provided an additional level of safety as they were not stored in the home after opening, unlike multi-use head lice treatments. Another Member noted that head lice products were commonly used on children while hair dye products were not.

The Committee noted the following mandatory labelling and packaging requirements for Schedule 6 and exempt neem products:

	Schedule 6 Neem Products	**Exempt Neem Products**
Container Requirements	The container must comply with Australian Standard AS 2216 – 1997 (Packaging for Poisonous Substances as published by Standards Australia) and if over 2 Litres nominal capacity must have POISON embossed or indelibly written on the side or shoulder of the container	The container must be fitted with a CRC
Labelling Requirements	"POISON" "KEEP OF OUT REACH OF CHILDREN" "FIRST AID" followed by "For advice, contact a Poisons Information Centre (*insert appropriate phone number*) or a doctor" and "If in eyes wash out immediately with water" The statement "Do not use if pregnant or likely to become pregnant" must be included immediately preceding the directions for use.	"Not to be taken" "Keep out of the reach of children" "Do not use if pregnant or likely to become pregnant"

The Committee agreed that the mandatory labelling and packaging requirements for Schedule 6 neem products conveyed a safety message to the consumer that this product needed to be stored with care and Members recognised that the additional requirement of a CRC may not be necessary on these products. The requirement for neem products exempt from scheduling to be packaged in a container fitted with a CRC and labelled with the required warning statements was seen as appropriate as exempt products were not subject to the same mandatory labelling and packaging requirements as Schedule 6 products. The current requirements placed on both the Schedule 6 neem products and the exempt neem products were seen to be comparable.

OUTCOME

The Committee agreed that the current SUSDP labelling and packaging requirement for *Azadirachta indica* (neem) remained appropriate.

13.4 AZADIRACHTA INDICA (NEEM)

PURPOSE

The Committee considered the definition of "debitterised neem seed oil" in Part 1 – Interpretation of the SUSDP.

BACKGROUND

The October 2002 and February 2003 NDPSC Meetings considered the scheduling of *Azadirachta indica* (neem). The Committee agreed that preparations containing *Azadirachta indica* neem or its extracts or its derivatives for human internal use be prohibited in Australia, except those containing "debitterised" neem seed oil. The Committee also agreed that products other than those for human internal use may remain available for sale to the public provided they are appropriately labelled and packaged. A definition of "debitterised neem seed oil" was created and included in Part 1 – Interpretation in SUSDP No. 17 Amendment No.3 (effective 1 May 2003).

Following the confirmation of the October 2002 scheduling decision on neem, it became evident that the definition of "debitterised neem seed oil" could create potential enforcement issues as the definition was broader than the term implied. Following consultation with the States and Territories, it was proposed that the definition should be amended to ensure clarity and to avoid potential enforcement problems.

DISCUSSION

The Committee agreed that the existing definition was not sufficiently specific and that the definition needed to specify that the highly purified oil must be sourced from the neem seed only.

DECISION 2003/38 - 21

The Committee agreed to amend the Part 1 - Interpretation entry in the SUSDP for "debitterised neem seed oil" from "… highly purified neem oil …" to "… highly purified oil from the neem seed …".

Part 1 – Interpretation - Amendment

"Debitterised neem seed oil" – amend entry to read:

"Debitterised neem seed oil" means highly purified oil from the neem seed containing only fatty acids and glycerides of fatty acids.

13.5 PSEUDOEPHEDRINE

PURPOSE

The Committee continued its consideration of the scheduling of undivided, combination and slow release (SR) preparations in Schedule 2 of the SUSDP.

BACKGROUND

The June 2002 Meeting agreed to reschedule all OTC single-active immediate release preparations from Schedule 2 to Schedule 3, and foreshadowed to consider the scheduling of remaining formulations at the October 2002 Meeting. However, preliminary information available at the October 2002 meeting did not provide sufficient evidence to support scheduling action on compounded, undivided and modified release pseudoephedrine preparations in Schedule 2. Nonetheless, the Committee remained concerned over the potential for the remaining Schedule 2 products to be diverted to the illicit drug trade and agreed that it would continue its consideration of the matter at the February 2003 meeting following further public consultation. This approach was viewed as an opportunity for the Committee to be informed of the outcome of ongoing investigations on all OTC pseudoephedrine products which was to be funded by the XXXXXXXXX, and for sponsors to indicate their plans for existing and future product lines.

The February 2003 Meeting agreed to defer further consideration of the scheduling of undivided, combination and slow release (SR) pseudoephedrine preparations in Schedule 2 to the June 2003 meeting to allow more time to review the findings of work commissioned by XXXXXXXXX, specifically the extractability of pseudoephedrine from various OTC formulations.

DISCUSSION

The Committee noted that pre-meeting submissions had been received from the following:

- XXXXXXXXX were opposed to any changes to the current scheduling of pseudoephedrine on the grounds that the agreements and recommendations arising from the last meeting of the National Working Group on the Diversion of Chemical Precursors (NWG) aimed at minimising the impact of pseudoephedrine diversion were likely to have a greater positive effect than rescheduling combination products to Schedule 3. XXXXXXXXX requested that the NDPSC encourage swift implementation of the recommendations to facilitate rapid impact of the proposed actions and to retain the current level of scheduling for pseudoephedrine products.
- XXXXXXXXX objected to the selective rescheduling of individual combination products as this merely shifts the focus of illicit users to other products which are not as strictly controlled. The company advised that there was a new compounded formulation of XXXXXXXXX currently under development and it was anticipated that a submission for this will be made to the TGA within the next 12 months. If the Committee was to consider any rescheduling of combination products, XXXXXXXXX considered that this rescheduling should apply to all pseudoephedrine products, including all modified release and combination products. However, the company would prefer that the NDPSC provided sufficient opportunity for the current national strategies and initiatives to take effect before taking further scheduling action.

- XXXXXXXXX reiterated its original position that it was essential to maintain a coordinated national approach and focus all efforts on ensuring compliance with the agreed strategies (ASMI Code of Conduct and the extraction research) and that any change in the current scheduling of pseudoephedrine at this time was unnecessary. Additionally, XXXXXXXXX advised that the research into pseudoephedrine extraction would be coordinated by the XXXXXXXXX and it was anticipated that it would be completed by the end of August 2003. It was expected this information would provide insight into the diversion of certain pseudoephedrine products for illicit use.
- XXXXXXXXX listed the following reasons why the NDPSC should not make any further changes to the current pseudoephedrine scheduling:

  (i) Scheduling alone would not reduce the supply of methylamphetamine to the illicit drag trade.

  (ii) Scheduling was not an appropriate mechanism for dealing with issues of diversion. Scheduling should be based on the safety profile of the substance and intended use.

  (iii) Pseudoephedrine was an essential medicine to which consumer access must be maintained, as there is no equally effective alternative available.

  (iv) There were no concerns of pseudoephedrine posing a risk to the legitimate purchaser.

  (v) The available data was not yet sufficient to determine the level of diversion.

  Additionally, the XXXXXXXXX considered that the problem of pseudoephedrine diversion could only be successfully addressed through a multi-faceted, cooperative and national approach and strongly encouraged the NDPSC to participate fully in such an approach. The XXXXXXXXX maintained that any further restriction of pseudoephedrine products was unjustified at this time and will not achieve the desired outcome.
- XXXXXXXXX supported the retention of undivided, combination and slow release preparations of pseudoephedrine in Schedule 2 on the basis that there was insufficient data for the Committee on which to base a scheduling decision at this time. The company believed that tighter scheduling of combination products would not control or prevent illegal behaviour and time was needed to assess the impact of the industry Code of Conduct and to determine if tighter scheduling of single active pseudoephedrine products has prevented their illegal use.

Members were reminded that *"Code of Conduct - Helping Prevent the Diversion of Non-Prescription Medicines Containing Pseudoephedrine"* (The Code) was granted interim authorisation by the Australian Competition and Consumer Commission (ACCC) on 13 February 2003 and the XXXXXXXXX indicated that it expected full authorisation to be obtained by late 2003. The Code sets minimum standards for the conduct of business for all marketers and manufacturers of pseudoephedrine containing medicines. The

XXXXXXXXX advised that the comments received by the ACCC regarding full authorisation of the Code had all been positive and that some minor changes had been made to The Code concerning the disposal and destruction of unwanted and expired stock. XXXXXXXXX also advised the Committee that it was involved in discussions with stakeholders concerning promotional activities in relation to Schedule 2 pseudoephedrine products.

The Committee was informed that the March 2003 meeting of the NWG had agreed to a series of measures:

- Pseudoephedrine was an essential ingredient in many medicines.
- The development and implementation of policies and codes of conduct to address diversion of pseudoephedrine and pseudoephedrine medicines required ongoing cross-sectoral and jurisdictional cooperation.
- Collaborative activities must continue to reinforce and promote awareness amongst pharmacies and the pharmaceutical industry.
- Research priorities, which should address the following key issues:
    1. What pseudoephedrine products are being diverted into the illicit drug manufacture of methylamphetamine?
    2. Does product formulation have any bearing on its selection for diversion into illicit drug production?
    3. What options are available for restriction of pseudoephedrine from retail outlets and subsequent diversion?
    4. Is there a requirement to treat all pseudoephedrine products in the same manner?

The NWG also made a number of recommendations in relation to:

- the disposal and/or destruction pseudoephedrine-containing medicines
- the security aspects of the storage and transport of drugs
- the provision of a national dataset of information on illicit drug production laboratories in Australia
- research into needs assessment of forensic laboratories across Australia (to be undertaken and funded by the Ministerial Council on the Drug Strategy)
- legislation or regulations to support the national Code of Practice for Supply Diversion into Illicit Drug Manufacture
- the development and implementation of a national early warning intelligence system on chemical precursors with the States and Territories feeding the necessary data to the Australian Crime Commission (ACC) in a standardised format to facilitate a national dataset

– Australia's continued involvement in international cooperation on preventing diversion of chemical precursors (assistance to regional countries, training and UN sponsored initiatives such as Project PRISM)

The Committee noted that the NWG was scheduled to meet in Canberra on 26 June and again in late September (in conjunction with the XXXXXXXXX). It was expected that the research coordinated by the XXXXXXXXX (due for completion by the end of August) will be discussed and that the outcomes of both the research and the NWG's meetings will be referred to the October NDPSC meeting for consideration.

Members advised that additional information regarding pseudoephedrine was sought from the Medicines Evaluation Committee (MEC) following the February 2003 NDPSC meeting. This included the approved indications and efficacy of products containing pseudoephedrine, if there was any scope to reduce the dosage of such products and if there was evidence of an increase in the number of applications to register combination products following the rescheduling of single active pseudoephedrine products in June 2002. XXXXXXXXX provided the following comments to the NDPSC which were later endorsed by the MEC at their meeting held on 5 June 2003:

- The approved indication for medicines containing pseudoephedrine is "nasal congestion", however claims appearing on labels may be more specific, relating to nasal congestion associated with colds and flu and hayfever.
- As pseudoephedrine is considered a long-established medicine, the TGA accepts standard references in place of clinical trial data as evidence of safety and efficacy to establish an effective dose.
- References such as Martindale, American Hospital Formulary Services (AHFS), the Handbook of Non-Prescription Drugs and the Australian Medicines Handbook recommend a dosage of 60 mg of pseudoephedrine every 4-6 hours with no references to a lower dose.
- In the 12 months to 30 June 2002, 23 applications for products containing pseudoephedrine were received by the TGA compared with 32 applications in the 12 months to 30 June 2003. 12 of the 32 applications were "clones" of other registered products and appear to be registered for reasons other than the change in scheduling for single-active pseudoephedrine products eg. marketing.

The XXXXXXXXX Member reported that the NWG had highlighted that the problem of pseudoephedrine diversion was widespread across the country and that an increase in the importation of pseudoephedrine products across State borders had been reported. This may be as a result of different measures adopted by individual States/Territories.

While the Committee acknowledged that any further scheduling decision concerning pseudoephedrine must be based on evidence, a Member noted that various State Police Departments had expressed concerns over the lack of police powers covering supply and possession of pseudoephedrine. Members agreed that the process of developing a national response to pseudoephedrine diversion was being progressed through the XXXXXXXXX.

The XXXXXXXXX Member reported that the Expert Advisory Committee on Controlled Drugs had considered pseudoephedrine at its last meeting and had made recommendations regarding the classification of pseudoephedrine under the New Zealand *Misuse of Drugs Act 1975*. The XXXXXXXXX Member agreed to refer the minutes of this meeting and their recommendations once they are confirmed for consideration by the NDPSC at the October 2003 meeting.

OUTCOME

The Committee agreed to defer any further scheduling consideration of pseudoephedrine until the October 2003 meeting to allow consideration of the outcomes of the extraction research and other measures agreed to by the National Working Group. The Committee also agreed to carry over all public submissions for pseudoephedrine from previous meetings.

13.6 THERAPEUTIC DEVICES

The Committee agreed to defer this item to a future meeting to allow sufficient time to examine the new device classification listings.

13.7 DEXTROMETHORPHAN

PURPOSE

The Committee considered including a total daily dose limit of 120 mg for all dextromethorphan preparations in Schedule 2.

BACKGROUND

The Committee considered dextromethorphan (a sustained release liquid preparation and inclusion of a 600 mg pack size limit) at the February 2003 NDPSC Meeting. The Committee agreed to amend the Schedule 2 dextromethorphan entry to include a 600 mg pack size limit of dextromethorphan for all preparations and to include a recommended daily dose of 120 mg or less of dextromethorphan for undivided preparations containing 0.6% or less of dextromethorphan. In addition, the Committee foreshadowed a new Schedule 2 entry that applied a total daily dose limit of 120 mg of dextromethorphan for all preparations. The purpose of this decision was to ensure that the sustained release (SR) product did not pose a greater risk of inappropriate use or accidental overdosage than the traditional immediate release (IR) products by keeping the daily dose limit uniform, irrespective of formulation.

DISCUSSION

The Committee noted the pre-meeting submission from XXXXXXXXX objecting to any further restriction of dextromethorphan products in the absence of any evidence of abuse. XXXXXXXXX stated that reports in the literature of dextromethorphan abuse are uncommon and there are few, if any, that are from Australia. General sale

dextromethorphan products available in New Zealand are primarily lozenges, which are less likely to be subject to abuse. XXXXXXXXX believes that as there does not appear to be a greater occurrence of abuse in Australia than in New Zealand, greater restriction in Australia is not justified at this time. Consequently, XXXXXXXXX supported the adoption of the New Zealand classification for dextromethorphan in Australia.

The Committee noted that the February 2003 NDPSC Meeting considered the harmonisation of the scheduling of dextromethorphan with New Zealand and agreed not to harmonise with New Zealand at that time. Dextromethorphan was subsequently included in the non-harmonised drug list for reconsideration in 2 years.

The Committee was informed that due to the limitations of the information on SIME, the regulatory impact of this proposed change could not be assessed prior to the June 2003 Meeting. However, the Committee noted that there were no post-meeting submissions received for the amendment made at the February 2003 meeting. The Committee agreed that the foreshadowed Schedule 2 amendment would provide a consistent approach for both divided and undivided preparations and minimise the potential for inappropriate use, abuse or accidental overdosage.

DECISION 2003/38 - 22

The Committee agreed to delete the recommended dose limit for divided preparations and include a recommended daily dose limit of 120 mg of dextromethorphan for all preparations in Schedule 2. The basis of this decision was to provide a consistent approach for all preparations covered by the Schedule 2 entry and to minimise the potential for inappropriate use, abuse or accidental overdosage.

Schedule 2 – Amendment

DEXTROMETHORPHAN - amend entry to read:

DEXTROMETHORPHAN when supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less of dextromethorphan.

13.8 MITRAGYNINE

PURPOSE

The Committee considered the foreshadowed inclusion of mitragynine and *Mitragyna speciosa* in Schedule 9 of the SUSDP.

BACKGROUND

The genus *Mitragyna* (Rubiaceae) occurs in West and East Africa, India and S.E. Asia. More than 30 different alkaloids have been characterised, and the majority of these are indole or oxindole structures. One alkaloid, mitragynine, isolated from *Mitragyna*

speciosa has analgesic and antitussive properties similar to those of codeine. It is also known as Kratom.

The February 2003 meeting agreed to foreshadow the inclusion of *Mitragyna speciosa* and mitragynine in Schedule 9 due to its pharmacological effect and potential for abuse. The leaves of *Mitragyna speciosa* have been referred to as an opium substitute.

DISCUSSION

The Committee noted that a pre-meeting comment was received from XXXXXXXXX, which stated that:

- there have been no recorded deaths or illnesses reported due to the use of this herb or extracts of it;
- the main alkaloid present in *Mitragyna speciosa* is mitragynine, a delta-opioid agonist, shown not to incur addictive patterns of abuse;
- the use of this herb outside of its native Thai area is little known and there is no established pattern of use; and
- recently in New Zealand, Kratom has been used effectively in treating patients going through Methadone addiction detoxification.

[Paragraph deleted]

The Committee noted the Therapeutic Goods Administration Laboratory Branch supported *Mitragyna speciosa* as the herbal species name and METHYL (αE,2S,3S,12bS)-3-ETHYL-1,2,3,4,6,7,12,12b-OCTAHYDRO-8-METHOXY-α-(METHOXYMETHYLENE)-INDOLO[2,3-a]QUINOLIZINE-2-ACETATE as the scientific name for mitragynine.

A member advised there are no listings for either mitragynine or Kratom being used in a clinical study or as a registered product in New Zealand.

The Committee noted that studies have showed mitragynine exerts agonistic effects on opioid receptors in in-vitro assays and also shows antinociceptive action (Tsuchiya S, Miyashita S, Yamamoto M, Horie S, Sakai S, Aimi N et al., European Journal of Pharmacolgy 2002;443:185-88). Furthermore Tsuchiya et al suggest that mitragynine has a morphine like action on gastric acid secretion in the central nervous system.

A member commented that tramadol, a mu-opioid receptor agonist included in Schedule 4 of the SUSDP, has a low potential for producing dependence. The Committee's attention was also drawn to an old publication which stated there were no addictive properties for mitragynine as may be found in morphine (Shellard E, Bulletin on Narcotics,1974;XXVI (2):41- 55). However it was noted from Micromedex Healthcare Series, Poisindex(R) Managements that addiction and withdrawal occur with chronic use of *Mitragyna speciosa.*

The Committee discussed further the abuse potential of mitragynine. Members were reminded that when a substance is brought to the Committee's attention that the Committee should act pro-actively, particularly when the substance fits the Schedule 9 requirements and there is an abuse potential. However the Committee was concerned whether there was not sufficient information to hand on the abuse and addiction potential and agreed to defer further consideration to the October 2003 meeting to enable additional information to be sought.

OUTCOME

The Committee agreed to defer further consideration of the scheduling of mitragynine and *Mitragyna speciosa* to enable additional information to be sought in regards to abuse and addiction potential.

13.9 NICOTINE REPLACEMENT THERAPY

PURPOSE

The Committee considered the advice received from the Department's Drug Strategy Branch (DSB) in relation to the scheduling Nicotine Replacement Therapy.

BACKGROUND

The February 2003 meeting considered the February 2002 *Urbis Keys Young* (UKY) Final Report entitled "Barriers to Access". This report related to investigations carried out to identify barriers to access of smoking cessation programs, nicotine replacement therapy (NRT) and other pharmacotherapies for the general Australian population and at-risk population groups. The report suggested that modifying the existing restrictions on the place of sale of NRT to allow availability in frequently accessed locations such as supermarkets had a clear potential to reduce barriers in accessing such products.

Whilst the Committee considered the report very informative, it was not clear on whether its recommendations were supported under the National Tobacco Strategy (NTS), from which the Committee could determine an appropriate course of action. On this basis, the Committee sought the advice of the DSB with regard to the place of NRT in the overall accepted national policy framework and strategy to reduce smoking in Australia.

DISCUSSION

[Paragraphs deleted]

OUTCOME

The Committee agreed to reconsider the scheduling of nicotine for use as an aid in smoking cessation at the October 2003 meeting under Trans-Tasman Harmonisation, and seek final advice from DSB on the place of NRT in the national policy framework and strategy to reduce smoking in Australia.

13.10 BUDESONIDE

PURPOSE

The Committee considered advice from the Medicines Evaluation Committee (MEC) concerning a warning statement proposed by XXXXXXXXX for intranasal budesonide products included in Schedule 3 of the SUSDP.

BACKGROUND

The NDPSC considered a rescheduling application for intranasal budesonide submitted by XXXXXXXXX at the October 2002 Meeting. The Committee agreed to amend the Schedule 3 entry for budesonide to extend the indications to include the short-term prophylaxis or treatment of perennial allergic rhinitis in adults and children 12 years and over. The Committee also considered XXXXXXXXX proposal for a warning statement on the product label "*If symptoms persist for more than 7 days, consult your doctor*". The Committee agreed to refer the proposed warning statement to the MEC for consideration as it was noted that there were no entries in Appendix F for any of the intranasal corticosteroids.

DISCUSSION

The Committee noted the MEC's advice that the Australian Guidelines for the Registration of Drugs – Volume 2 (AGRD2) policy guideline on corticosteroid nasal sprays requires the warning "*See your doctor or pharmacist if symptoms are not relieved within 7 days*" to be included on either the product label or the Consumer Medicine Information (CMI) leaflet on all Over-The-Counter (OTC) corticosteroid nasal sprays, including budesonide. If the required information is included only in the CMI, the CMI must be provided as a pack insert and the label must include the statement "*Read the enclosed Consumer Medicine Information leaflet before starting to use this product*". The MEC also noted in their correspondence that the guideline for corticosteroid nasal sprays was developed in response to a request from the NDPSC when these products were first included in Schedule 3 of the SUSDP to ensure that the warning statements were consistent with those required in New Zealand.

OUTCOME

The Committee accepted the MEC recommendation and agreed that the proposed warning statement not be included in Appendix F of the SUSDP on the basis that TGA guidelines (AGRD2) already require a similar statement on the labelling or CMI of all OTC nasal spray products.

13.11 SODIUM PHOSPHATE

PURPOSE

The Committee considered comment received from XXXXXXXXX regarding sodium phosphate bowel cleansing preparations.

BACKGROUND

XXXXXXXXX markets a product, XXXXXXXXX, containing 2.4 g sodium phosphate monobasic and 0.9 g of sodium phosphate dibasic per dose of 5 mL and packed in a 45 mL bottle. The product is indicated for use in bowel cleansing and is covered by the current Schedule 3 entry for sodium phosphate.

The June 2002 meeting considered an application by XXXXXXXXX to include macrogol 3350 and sodium picosulfate for laxative use in Schedule 4, for consistency with sodium phosphate, and list all three substances for use in bowel cleansing in Appendix H of the SUSDP. The Committee agreed to foreshadow the inclusion of these substances when in preparations for laxative use in Schedule 4, however the Committee did not support inclusion of sodium phosphate, sodium picosulfate and macrogol 3350 for use in bowel cleansing in Appendix H. The Committee considered brand advertising of sodium phosphate, sodium picosulfate and macrogol 3350 for bowel cleansing purposes not to be appropriate on the basis that the specified Schedule 3 indication was not appropriate for advertising and that no significant case was made in the submission to support the proposal to list sodium phosphate, sodium picosulfate and macrogol 3350 in Appendix H. The Committee also noted the August 2000 minutes concerning the decision not to include macrogol 3350 in Appendix H. These minutes indicate that the reason for this decision was that there appeared to be no public health benefit associated with including macrogol 3350 in Appendix H, a requirement that must be fulfilled under the NCCTG Guidelines.

The February 2003 NDPSC Meeting considered a further application from XXXXXXXXX to include sodium phosphate in Appendix H and rejected the proposal on a number of grounds.

The NDPSC Secretariat sought comment from XXXXXXXXX prior to the February 2003 NDPSC Meeting on the subject of advertising of bowel cleansing preparations and received their reply in early April.

DISCUSSION

The Committee noted that the correspondence from XXXXXXXXX stated that the majority of gastroenterology units either provided the preparation to be used for bowel cleansing prior to colonoscopy procedures in conjunction with suitable instructions or recommended the preparation at the time when instructions were provided. A straw poll of executive members of the XXXXXXXXX showed that there was an approximate 50:50 split between these two alternatives. XXXXXXXXX stated that there were no

circumstances where the choice of preparation was left to the patient or the pharmacist. Invariably, the doctor performing the colonoscopy had a standard protocol best suited to his practice. XXXXXXXXX considered that this indication was not suitable for public advertising and that such advertising may encourage inappropriate use resulting in considerable risks to patients such as electrolyte disturbance and cardiac and renal complications.

OUTCOME

The Committee noted with interest the correspondence from XXXXXXXXX..

13.12 LANSOPRAZOLE

PURPOSE

The Committee considered correspondence from XXXXXXXXX in relation to the decision of the February 2003 NDPSC meeting not to reschedule small packs of oral lansoprazole to Schedule 3.

BACKGROUND

Lansoprazole is a proton pump inhibitor similar to omeprazole (Schedule 4) and pantoprazole (Schedule 4). It binds irreversibly to the proton pump on the mucosal membrane of the gastric parietal cells which inhibits gastric acid secretion, reduces the pH (acidity) of the gastric fluid, and thus reduces the pain associated with the reflux of gastric fluid into the lower oesophagus.

XXXXXXXXX markets two lansoprazole products, XXXXXXXXX and XXXXXXXXX, for the treatment and long-term management of patients with duodenal ulcer, benign gastric ulcer and reflux oesophagitis. Lansoprazole was first considered for scheduling at the April 1994 meeting where it was included in Schedule 4.

The February 2003 NDPSC Meeting considered an application from XXXXXXXXX to reschedule lansoprazole in oral dose forms containing not more than 30mg from Schedule 4 to Schedule 3 for the relief of symptoms of gastro-oesophageal reflux (heartburn) and acid-related dyspepsia (indigestion) in packs containing not more than 14 days supply. Inclusion in Appendix H was also sought. The Committee rejected the proposal on the following grounds:

- Based on the data submitted, the Committee accepted that the potential for adverse events was low following treatment of gastro-oesophageal reflux disease (GORD) with lansoprazole and that it was unlikely that the safety profile would be significantly altered when used as an OTC medicine with the wider indications. However, the Committee noted that no safety data was submitted for OTC use for these wider indications including heartburn and dyspepsia.

- The Committee was not provided with sufficient evidence of efficacy for use in treatment of the symptoms of heartburn and dyspepsia as opposed to the treatment of GORD.
- The proposed indications for use, onset and duration of action were more appropriate to the prevention of symptoms rather than intermittent treatment of, or relief from, symptoms.
- There was a need to address appropriate alarm symptoms requiring medical investigation rather than ongoing intermittent self-medication.

DISCUSSION

XXXXXXXXX provided comment on the Record of Reasons for the February 2003 NDPSC Meeting concerning lansoprazole. XXXXXXXXX also sought independent opinion from Australian clinical experts in the field of gastroenterology on a number of the points made at the meeting. Although the correspondence cannot be considered as a post-meeting submission (under regulation 42ZCZ) as there was no scheduling amendment made at the February 2003 meeting in relation to lansoprazole, XXXXXXXXX requested that the Committee consider its response with a view to setting aside the February 2003 decision ie that the inclusion of lansoprazole in Schedule 4 remained appropriate at this time. XXXXXXXXX submission was also referred to the evaluator of the initial rescheduling application for comment.

XXXXXXXXX has raised the following points relating to the Record of Reasons:

- Heartburn and dyspepsia are symptoms of GORD and the use of proton pump inhibitors (PPI's) in the OTC treatment of the symptoms of GORD and heartburn and/or dyspepsia is supported by the clinical trial datset. These data has been previously evaluated by the TGA at registration and was seen as sufficient to support lansoprazole's efficacy for the proposed Schedule 3 indication.
- The symptoms of GORD do not require medical diagnosis. There is a long history of self-diagnosis and self-treatment of heartburn and indigestion by patients.
- Lansoprazole is suitable for short-term, intermittent self-medication.
- PPI's have been shown to be at least fast, and often faster than, the H_2RAs.
- The Guidelines from Gastroenterology Society of Australia (GESA) recommended the use of PPI's as first-line agents in the treatment of GORD.
- Lansoprazole's drug-drug interaction profile is superior to antacids and the H_2RA cimeidine. Substantial evidence was submitted with the original rescheduling application to support this.
- The percentage of patients where relief may take up to 4-5 days to be achieved is small and, based on the data included with the application and from the literature, this percentage is comparable with that for H_2RAs.

- A pharmacist education program provided by XXXXXXXXX was proposed. This would be aimed at providing pharmacists and pharmacy assistants with an understanding of the benefits of lansoprazole in the treatment of heartburn and indigestion, an appreciation of the issues that are important in counselling patients prior to the purchase of lansoprazole, and a clear understanding of the distinctions between common symptoms of dyspepsia and those of more serious conditions such as angina, gastric ulcerations and gastric carcinomas.
- XXXXXXXXX had no objections to amending the CMI to include "alarm" symptoms and warning statements as outlined by the Committee.
- Short-term, symptomatic use does not pose a significant risk of masking more serious disease and would be no different to the H_2RAs in this respect.
- Although pharmacokinetics data suggested a possible interaction of lansoprazole with the administration of food, any such effect has not been demonstrated to be clinically significant.
- The evaluator agreed that lansoprazole has a favourable safety profile and has a low potential for abuse which XXXXXXXXX has seen as inconsistent with some of the adverse statements included in the report.
- XXXXXXXXX felt it was unreasonable and unnecessary to conduct a self-diagnosis study, a usage study and a multicultural study given that the plethora of OTC products available to treat the indication being sought. A comprehensive label study was not warranted as a review of the current labels for OTC products such as the H_2RAs and antacids was undertaken in the development of the proposed OTC lansoprazole label.
- The awareness of a very effective alternative to the current OTC products used for the treatment of reflux and heartburn (symptoms of GORD) is important to realise benefits to consumers and the community such as the prevention of progression to erosive oesophagitis and the avoidance of costly hospitalisation. Inclusion of lansoprazole in Appendix H of the SUSDP would achieve this.

The evaluation report stated the following in response to the issues raised by XXXXXXXXX:

- The evaluator noted that the definition of GORD was a pivotal issue in the consideration of the application. Guidelines from learned societies and independent organisations such as the National Institute for Clinical Excellence (NICE) in the UK distinguished between patients with GORD and those with intermittent symptoms of dyspepsia and/or heartburn. In contrast, the sponsor contended that the proposed indication for Schedule 3 availability of lansoprazole defined a group of patients who represented a subset of GORD. The evaluator considered that patients with intermittent symptoms of heartburn may be regarded as having intermittent gastro-oesophageal reflux, but not GORD and as such, the GESA guidelines would not apply in this situation. While PPI's were clearly the drugs of choice in the treatment of GORD, the use of PPI's for the treatment of less frequent and/or less specific symptoms of dyspepsia and/or heartburn is less clear. The evaluator considered that the sponsor was over-simplifying the case by claiming that patients with "dyspepsia

and/or heartburn" represent a subset of GORD and felt it would be more accurate to say that patients with GORD represent a subset of the population with dyspepsia and/or heartburn, both of which may also be due to other conditions unrelated to gastro-oesophageal reflux such as peptic ulcers, oesophagitis, cancer of the stomach or pancreas and gallstones.

- The evaluator did not dispute that lansoprazole was effective in treating the symptoms of GORD. However, the issue was whether or not a PPI was an appropriate treatment in the context of intermittent, self-diagnosed "symptoms of gastro-oesophageal reflux (heartburn) and acid-related dyspepsia (indigestion)" which may or may not be related to gastro-oesophageal reflux. The NICE advises that patients with mild reflux symptoms, particularly when there is no proven pathology, can frequently be managed by alternative therapies in the first instance, including antacids, alginates or H_2RAs and should not be routinely treated with PPI's when diagnosed with non-ulcer dyspepsia. Regardless of whether the patient is treated on a step-up basis (antacids first, then if unsuccessful H_2RAs, then if unsuccessful PPI's) or a step down basis (the opposite approach), neither group should be treated with PPI's on a long-term basis without a definite clinical diagnosis being made. Although the sponsor proposed labelling and educational programs aimed at reducing the risk of long term treatment with PPI's, the OTC availability of lansoprazole would nevertheless increase this risk.
- While the British Society of Gastroenterology's Dyspepsia Management Guidelines state that the best relief is provided by PPI's, they recommend explicitly that the NICE guidance on PPI's should be followed. Lansoprazole may not be an appropriate first-line management strategy for consumers with non-specific heartburn and dyspeptic symptoms, primarily on the grounds of higher cost to the community, and is therefore best reserved for use on a prescription basis following evaluation of the symptoms by a medical practitioner.
- The evaluator acknowledged that the recent Cochrane review comparing approaches to the management of non-specific dyspepsia did provide evidence that there may be a higher response rate to PPI's than to H_2RAs in this context. However, the Cochrane review on heartburn reported that although PPI's had significant advantages over H_2RAs in endoscopy-positive GORD, there was no difference between the drug groups in endoscopy-negative disease, which was more likely to represent the group of patients self-medicating.
- The sponsor proposed to address the issue of patients with lesser symptoms, but more severe mucosal damage and whose treatment needed to be under medical supervision by providing an educational program to pharmacists. Since the education program was designed to inform pharmacists about symptoms associated with more severe conditions, it was unlikely to achieve the stated aim of safeguarding those patients with severe mucosal damage and few symptoms. It was be reasonable to assume that pharmacists would have a similar ability to that of medical practitioners to make judgements concerning referral. This would be true if the indications for endoscopic investigation recommended by the British Society of Gastroenterology were applied (new dyspepsia in patients aged over 55 years and/or presence of "alarm" symptoms).

- The sponsor considered the evaluator's comment concerning the administration of lansoprazole on an empty stomach highly selective and ignored other data, however there were no data that demonstrated a lack of pharmacokinetic interaction with food. The comment originated from data that demonstrated that despite the reduction in bioavailability of lansoprazole in the presence of food, its clinical efficacy was not reduced. This was likely to be related to the dosing of lansoprazole in the upper part of the dose-response curve such that a reduction in bioavailability had little effect on the degree of proton pump inhibition. The initial assertion, that a better effect per mg of dose would be achieved with lower doses taken on an empty stomach, still stands.
- The evidence provided in the original application had not convincingly demonstrated the superiority of lansoprazole over more recently developed H_2RAs and antacids in relation to drug interactions. The claim of rapidity of onset of effect was not substantiated in the context of intermittent transient therapy (as proposed) as the studies comparing lansoprazole and H_2RAs compared at least 4 weeks of daily therapy with the onset of relief of symptoms measured in days rather than hours.
- No evidence was provided in the original application to support the need for lansoprazole to be advertised directly to the consumer. The prevention of progression to erosive oesophagitis can certainly be regarded as a benefit to the consumer, but in the group for whom the OTC treatment was intended, it was unlikely that this would be realised very often since these individuals were much more likely to have endoscopy-negative disease. The suggested benefits to consumers could be realised by ensuring that pharmacists were aware of the availability of lansoprazole, rather than exposing consumers to potentially confusing advertising. The GESA guidelines recommended the use of PPI's as initial treatment for GORD, however this recommendation was not relevant to the patients included in the proposed indication. The NICE guidance specifically stated that "patients with mild GORD symptoms and/or those who do not have a proven pathology can frequently be managed by alternative therapies (at least in the first instance) including antacids, alginates or H_2RAs". The sponsor's response did not provide a cogent argument for including lansoprazole in Appendix H of the SUSDP.
- Many of the points argued in the pre-meeting comments section of the sponsor's response have been discussed above. The evaluator emphasised that the sponsor's repeated view that "symptoms of heartburn and dyspepsia are a subset of GORD" was over-simplified and misleading. Given that many individuals with heartburn and dyspepsia have conditions other than GORD, it was clear that GORD was a subset of heartburn and dyspepsia, representing the severer end of the spectrum of symptoms arising from gastro-oesophageal reflux which in itself was a physiological event.
- The evaluator did not dispute the efficacy of PPI's in the treatment of GORD, however the role of PPI's for intermittent use in self-diagnosed heartburn and dyspeptic symptoms was controversial. The sponsor's response had not altered the view of the evaluator that the rescheduling of lansoprazole from Schedule 4 to Schedule 3 was premature at this time.

The evaluator also noted that XXXXXXXXX had not revealed the identity(ies) of the expert(s) from who they sought clinical comment and it was not indicated whether or not

the respondents were expressing a personal opinion or representing a learned society such as GESA which would have been an appropriate source of independent comment. It would also have been appropriate for the response to have included a statement by the commenting experts to indicate whether or not they had any potential conflict of interest such as membership of any advisory committees set up by the sponsor, receipt of any financial sponsorship from the sponsor to support clinical or research activities or to attend conferences etc. The evaluator considered the provision of expert advice without ensuring transparency and independence in this manner was inappropriate. Accordingly, the clinical expert advice was not weighted as highly as it would otherwise have been by the evaluator.

The Committee noted that the GESA Guidelines stated that there was a move toward the use of high level or more potent initial therapy for the treatment of reflux disease for the majority of patients and that the traditional 4-week course of PPI treatment was considered appropriate. This was twice the duration of treatment sought for the proposed indication (not more than 14 days). The Guidelines acknowledged that a 2-week treatment may be sufficient, however this required further research. The Committee also noted that the Guidelines stated that "the high level therapy approach was not considered appropriate for individuals whose reflux-induced symptoms were not severe enough to meet the definition of reflux disease" ie "when reflux exposes the patient to the risk of physical complications or symptoms lead to a significant impairment of well-being or quality of life (symptoms occurring on two or more days a week)".

The Committee noted that the GESA Guidelines stated that long-term PPI therapy in the presence of *H.pylori* infection increased the risk of gastric mucosal atrophy while eradication therapy reduced this risk. The Guidelines also stated that in some patients, *H.pylori* eradication improved heartburn symptoms. As *H.pylori* infection and eradication therapy required medical intervention, the Committee was of the view that the use of PPI's may not be advisable prior to consultation with a doctor.

Members considered that while the submitted data provided evidence on the efficacy of lansoprazole for the treatment of GORD, they did not adequately demonstrate that this substance is an appropriate self-medication treatment for the short-term relief of symptoms of dyspepsia and heartburn. The data submitted indicates that lansoprazole works best as an ongoing preventative measure rather than a one-off treatment for the relief of symptoms once they have occurred. It was considered that data on the proposed OTC use of lansoprazole were required to allow the Committee to make an assessment on whether this is an appropriate indication for inclusion in Schedule 3.

OUTCOME

The Committee agreed that correspondence from XXXXXXXXX seeking reconsideration of the February 2003 decision concerning lansoprazole did not alter its previous assessment and that the inclusion of lansoprazole in Schedule 4 of the SUSDP remained appropriate at this time for the following reasons:

- The data submitted were not considered adequate to support the proposed use of lansoprazole as an appropriate Schedule 3 medicine for intermittent, short-term treatment of the symptoms of heartburn and dyspepsia.
- The proposed indications for use, onset and duration of action were more appropriate for the prevention of symptoms rather than intermittent treatment of, or relief from, symptoms. There is also an increased risk of masking more serious conditions if lansoprazole is taken as first-line treatment prior to medical assessment given the overlap in symptoms. Treatment with alternative therapies such as antacids, alginates or histamine-2 receptor antagonists (H_2RA) may be appropriate in the first instance.
- There is no significant difference between the use of proton pump inhibitors (PPI's) and H_2RAs in the treatment of heartburn for endoscopy-negative disease, which is more likely to represent the group of patients self-medicating.
- The NICE advises that patients with dyspepsia should not be treated with PPI's on a long-term basis without a definite clinical diagnosis being made by upper gastrointestinal endoscopy where appropriate.
- The GESA Guidelines stated that long-term PPI therapy in the presence of *H.pylori* infection increased the risk of gastric mucosal atrophy while eradication therapy reduced this risk. As *H.pylori* infection and eradication therapy required medical intervention, the use of PPI's should not be advised prior to consultation with a doctor.

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

14.1 SUSDP, PART 4

14.1.1 ORLISTAT

This item was withdrawn XXXXXXXXX.

14.1.2 IBUPROFEN

PURPOSE

The Committee considered an application seeking exemption from the scheduling requirements of divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 24 or less dosage units when labelled with a maximum recommended daily dose of 1200 mg of ibuprofen.

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 listed in Schedule 4 of the SUSDP at the February 1973 meeting. Subsequently at the May 1989 meeting ibuprofen was included in Schedule 3, in packs of 24 or less tablets or capsule for the relief of dysmenorrhoea or of pain associated with inflammation. The Schedule 3 entry was amended at various meetings until the May 1995 meeting when a new Schedule 2 entry was proposed. At the May and August 1998 meetings, the Committee considered exempting ibuprofen from scheduling in divided dosage units containing 200mg or less of ibuprofen per unit in pack sizes of 24 or less but decided that there should be no change to the scheduling due to the safety concerns associated with the wider availability of another NSAID for use as an analgesic. Ibuprofen is currently available for oral use in Schedules 2 and 4 of the SUSDP. At the October 2002 meeting the NDPSC exempted ibuprofen for external use from scheduling on the basis of the available safety data.

DISCUSSION

The Committee noted XXXXXXXXX proposed divided preparations containing up to 200 mg of ibuprofen , and no other active ingredient, in pack sizes up to 24 dosage units, and labelled with a recommended daily dose of 1200mg and appropriate warnings, be exempt from scheduling. XXXXXXXXX made the following points in its submission:

- Ibuprofen in divided preparations for oral use has been available without prescription in Australia, initially in Schedule 3 and more recently Schedule 2, since 1989.
- Headache is the most common indication for which consumers purchase analgesics with most purchasers being generally well, healthy individuals aged between 25 and 44 years.
- Ibuprofen prescription products intended for chronic use in doses up to 2400 mg daily have a different indication than those products intended for self-selection, short term use and mild to moderate common pain states.
- Ibuprofen 200mg tablets have been available in small packs without prescription for general sale in the USA and UK since 1984 and 1996 respectively, without any increase in the incidence of adverse effects.
- Ibuprofen has a better safety record than other NSAIDs, (including naproxen, aspirin and diclofenac) that are non-prescription medicines particularly in relation to gastrointestinal (GI) toxicity. Ibuprofen has a wide margin of safety, particularly in overdose situations, unlike paracetamol.
- Ibuprofen has no effect on cardiovascular parameters when taken according to the directions for OTC use.
- Ibuprofen has a short half-life and linear pharmacokinetics, contributing to its safety profile in overdose.

- Worldwide OTC availability and consumption of ibuprofen in non-prescription formats suggest that consumers, health care professionals and regulators regard ibuprofen as effective and useful analgesic with a safety profile suitable for OTC (general sale) use.
- Consumers would benefit from the availability of a safe and effective product with both analgesic and anti-inflammatory properties, given that their current choices are limited to products with analgesic effects only (paracetamol) or an anti-inflammatory drug with a significantly worse GI safety profile than ibuprofen (aspirin).
- It is proposed that the warning statements for ibuprofen when included in Schedule 2 are managed through the Therapeutic Goods Administration (TGA) registration process rather than the SUSDP.

The Committee noted the following issues were raised in the evaluation report of the submission which was prepared for the Committee:

- Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with a good safety record relative to other NSAIDs and relative to aspirin and paracetamol, both of which are analgesic/antipyretics available for general sale.
- Ibuprofen has a very low to absent potential for abuse.
- The indications for low dose (≤ 1200mg/day) oral administration of ibuprofen are suitable for self-identification and treatment without professional advice. However attention to the wording of the indications on the packaging is required to ensure the meaning is clear.
- Ibuprofen products have been available for general sales in the USA since 1984 and in the UK since 1996, with no significant safety issues arising over that time.
- There is considerable OTC marketing experience within Australia under S3 & S2, and the spontaneous reporting rate of adverse events has been very low. Trial evidence and post-marketing surveillance suggest that low dose ibuprofen is safe in OTC use.
- The submission referred to the PAIN study, 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 adults in general practice (N Moore et al, Clin Drug Invest, 1999;18(2):89-98). The results indicated that ibuprofen was tolerated as well as paracetamol and significantly better than aspirin. Gastrointestinal adverse effects were no higher for ibuprofen than for paracetamol.
- There is reasonable evidence to show that ibuprofen, used intermittently in low doses for small pack sizes, is as well tolerated as paracetamol, better tolerated than aspirin and safer than paracetamol in overdose. De-scheduling is unlikely to lead to any public health concerns, and it would provide consumers with an additional choice of simple analgesic product available at general outlets.
- The evaluator recommended that single active divided preparation of ibuprofen 200mg or less when packed in blister or strip packaging of not more than 24 dosage units are de-scheduled.

The Committee also noted that XXXXXXXXX subsequently provided a new publication identifying the risk factors for adverse events in analgesic users from the PAIN study (N Moore et al, Pharmacoepidemiology and Drug Safety, 2003;12:1-10) to support their application. The Evaluator found that the additional reference did not alter the evaluation or the conclusions. However the Committee acknowledged that the PAIN study excluded patients with contraindications.

The Committee noted pre-meeting comments were received from the persons listed in Attachment 1.

The Committee addressed XXXXXXXXX letter, drawing attention to a recent XXXXXXXXX advertisement in the pharmacy trade media. The Committee agreed that as this was an advertising complaint it was a matter for consideration by the appropriate advertising compliants panel.

The Committee acknowledged receipt of the XXXXXXXXX booklet *NSAIDS, coxibs & aspirin for inflammatory and other connective tissue disorders* (2003). The XXXXXXXXX pointed out that none of these medications are without risk and that persons selling, prescribing or using these substances should conduct a safety assessment.

The Committee was provided with the XXXXXXXXX. Pharmacists were asked to estimate the number of times they had intervened in particular types of supply of ibuprofen in the last three months as well as the number of times they had suggested alternative treatments and/or referred consumers to their doctor. It was noted that 869 pharmacy responses were analysed:

- 87% had intervened in potential drug interactions;
- 93% had intervened in cases where the person was already taking a prescription NSAID;
- 74% had intervened in the supply to a pregnant woman;
- 88% had intervened in the supply to person with a known contraindication;
- 94% had suggested alternative treatment; and
- 87% had referred the person to their doctor.

A Member commented that the XXXXXXXXX survey was a retrospective targeted survey and considered a survey based on cross sections of the community would have been more constructive to the consideration. Another Member advised that pharmacists believe they do make a difference by advising consumers on the quality use of medicines and do help prevent adverse events. The Member acknowledged that the retrospective nature of the XXXXXXXXX survey limits its usefulness. In some cases the pharmacist may guide a consumer to take ibuprofen as an anti-inflammatory, if its use is more appropriate. Whilst the short term use is considered to be safe and efficacious the Member argued that by making ibuprofen more widely available, it could be used more long term. It was underlined by that Member that increased uncontrolled exposure to NSAID is not safe, a point raised by many of the pharmacy submissions.

A Member was concerned with the concomitant use of NSAIDs and ACE inhibitors given the results from the PAIN study identified the number and nature of concomitant medication as the main risk factors for adverse events in analgesic users. Another Member advised that from clinical experience interactions with the chronic use of ibuprofen at higher dosages have been seen and interactions with short-term use of ibuprofen are unlikely to occur. There was also no apparent issue of an increase in spontaneous adverse events reported in the US and UK since general sales were available.

Another Member stressed this application was for intermittent use for self-limiting and self-treatable indications in a small pack size. It provided another access option, through general sale, and appropriate warning statements were included on the label. The Member informed the Committee that XXXXXXXXX have also agreed to establish a 1800 telephone number for consumers to access additional information as required.

The Members were informed that in New Zealand current use of analgesics is weighted heavily towards paracetamol and the argument presented against general sales of ibuprofen was it would increase the total number of NSAID users and thus would increase the risk of adverse events. This does not appear evident from the considerable international marketing experience with ibuprofen.

The Committee's attention was drawn to s52E of the *Therapeutic Goods Act 1989* (the Act), particularly Subsection (1)(f) the need for access to a substance, taking into account its toxicity compared with other substances available for a similar purpose. It was accepted that when used intermittently in low doses and small packs, ibuprofen is as well tolerated as paracetamol, better tolerated than aspirin, and safer than paracetamol in overdose.

The Committee noted there are approximately 45 products on the ARTG which contain 200 mg or less of ibuprofen as the only active ingredient, in a tablet or capsule, with various pack sizes and one 200mg ibuprofen product in a sachet. The Committee noted that the sachet was the same strength as the tablet or capsule and considered it appropriate to consider exempting the sachet presentation as well. The Committee agreed that the schedule wording would need to be comparable to the current aspirin and paracetamol entries. For consistency the Committee agreed it was appropriate to raise the pack size to 25, taking into account these entries.

Whilst the Committee was cognisant of Medicines Evaluation Committee's (MEC) proposal (Item 17.1) to recommend changes to warning statements for ibuprofen in Appendix F of the SUSDP, the Committee thought it appropriate to proceed with the current submission using the existing Appendix F warning statements and taking into account the proposed Australian Regulatory Guidelines for OTC medicines.

DECISION 2003/38 - 23

The Committee agreed to exempt divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 25 or less dosage units when labelled with a maximum recommended daily dose of 1200 mg of ibuprofen from scheduling.

The Committee took into account Section 52E of the *Therapeutic Goods Act 1989*, the labelling, packaging and presentation of a substance and the relevant Guidelines for the NDPSC. The Committee agreed that

- The proposed indication and the product are suitable for self-identification and self-treatment without professional advice;
- The safety profile of low dose ibuprofen in the OTC setting is good;
- A comparison with similar unscheduled analgesic products (aspirin and paracetamol in small pack sizes) indicated that short term intermittent use of low dose ibuprofen had a relatively good safety profile.
- Ibuprofen administered orally has been demonstrated to have a wide therapeutic index and the risk masking a serious disease is very low
- Ibuprofen has a very low to absent potential for abuse.
- There is considerable OTC marketing experience in Australia as well as considerable international marketing experience with prescription, pharmacy and general sales. The spontaneous reporting rates of adverse events in Australia and overseas has also been low.

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 100 or less 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 of 25 or less dosage units;

(iv) the primary pack is labelled with the warning statement to the following effect:

WARNING - This medication may be dangerous when used in large amounts or for a long time (period);

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful; or

CAUTION - This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged or excessive use without medical supervision could be harmful;

(v) the primary pack is labelled with the warning statement to the following effect:

Do not use during the last three months of pregnancy;

(vi) the primary pack is labelled with the warning statement to the following effect:

Ask your doctor or pharmacist before use if you have asthma; or

Most asthmatics can take/use products containing ibuprofen, but if you are sensitive to ibuprofen, aspirin or other medicines for pain relief, do not take this product. If you are unsure, consult your pharmacist or doctor; and

(vii) the primary pack is labelled with the warning statements to the following effect:

Do not take/use if you are allergic to aspirin, ibuprofen, or other medicines for pain relief;

Do not use in the presence of a stomach ulcer or other stomach disorders, impaired kidney function or heart failure; and

Ask your doctor before use if you are pregnant or are taking anticoagulant medication, medication for

high blood pressure, diuretics, lithium,
methotrexate or other medicines for pain relief.

Schedule 4 - Amendment

IBUPROFEN - amend entry to read:

IBUPROFEN **except**:

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

(b) in preparations for dermal use.

14.1.3 NICOTINE

PURPOSE

The Committee considered an application seeking to reschedule nicotine lozenges to Schedule 2 of the SUSDP.

BACKGROUND

In Australia, XXXXXXXXX markets XXXXXXXXX, containing 2 mg and 4 mg of nicotine. These products are indicated on the Australian Register of Therapeutic Goods (ARTG) for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. If possible, when stopping smoking, should be used in conjunction with behavioural support program.

The August 2001 NDPSC meeting considered an application from XXXXXXXXX seeking to include XXXXXXXXX in Schedule 2. The NDPSC agreed to include nicotine lozenges, for use as an aid in withdrawal from tobacco smoking, in Schedule 3 of the SUSDP, given that the pharmacokinetic and safety profile, and toxicological properties of the lozenge formulation was expected to be similar to the sublingual tablets. It was also agreed that the differences in use pattern of nicotine replacement therapy (NRT) products and the pharmacokinetic profile of nicotine lozenges warranted initial and on-going professional advice/counselling for the appropriate use, to enhance consumer success in ceasing tobacco smoking and to manage any consequent adverse events. In the absence of clinical experience with the lozenge formulation, a 'staged' approach was considered appropriate before allowing the preparation into a more open market. Subsequently, at the November 2001 meeting the Committee confirmed this scheduling decision. The Committee also agreed that the risk of access to nicotine lozenges by children in the home and the potential for overdose, given the higher bioavailability of nicotine from lozenges compared with gum, remained a concern as there was no local or overseas post-marketing experience.

DISCUSSION

The Committee noted XXXXXXXXX had submitted a further application to reschedule XXXXXXXXX from Schedule 3 to Schedule 2. The applicant highlighted the following in support of its proposal:

- Smoking is the single largest cause of preventable death in Australia and quitting smoking has major health benefits for individuals and the community.
- NRT is effective in helping a person to quit smoking, approximately doubling the chance of quitting successfully.
- NRT is available in a wide range of formats including chewing gum, transdermal patch, inhalers, sublingual tablets (not marketed in Australia), and inhaler device and in lozenge form, which provides an alternative for people who prefer to use oral therapy but are unable to use chewing gum.
- The efficacy and safety of XXXXXXXXX has been established in a clinical development program and the safety profile for the lozenge preparation was similar to that for other NRT products. The safety profile was supplemented by safety data from worldwide post marketing surveillance.
- The use of the time to first cigarette in the morning (TTFC) as a measure of the degree of nicotine dependence and therefore a basis for dose selection would facilitate its correct use as a Schedule 2 medicine. Pharmacist advice would be available if required.
- There is a public need for wider availability of various NRT's to assist smokers to quit and therefore to improve the health and community as a whole. The increased availability of NRT OTC is likely to increase utilisation by smokers wishing to quit.
- Smokers are reluctant to approach a Pharmacist for advice regarding NRT and the ability to self-select would increase the number of smokers accessing the lozenge preparation and thus increase the quitting success rate.
- The application addresses the NDPSC concerns from the August 2001 and November 2001 meetings.

The Committee noted the evaluation report stated:

- NRT is well established as an effective approach to assistance for smoking cessation in nicotine-dependent smokers. The indication and provision of nicotine by various routes have been accepted as suitable for OTC use.
- Clinical experience with lozenges has been acquired, since 2001 scheduling consideration, to provide more confidence that the product is safe in OTC use.
- The indication, " a treatment-aid to smoking cessation for the relief of tobacco withdrawal symptoms", meets the criteria for a suitable indication for a Schedule 2 product.

- The safety profile of the nicotine lozenge shows a low frequency of adverse events that are generally minor and similar in frequency, type and severity to those reported with other NRT products including chewing gum. The contraindications to NRT are identical to those for nicotine chewing gum and would be readily understood by consumers. The proposed labelling includes appropriate warning statements and the proposed consumer medicine information includes clear contraindications statements.
- No evidence is provided to support the argument that more smokers, who would have failed to access NRT, will access treatment and cease smoking. However it is reasonable to assume that the more readily available a NRT is, the more people may access it.
- Marketing experience, both within Australia and overseas, show the spontaneous reporting rate of adverse events has been very low. Post-marketing surveillance, both by ADRAC and a sponsor initiated worldwide program has indicated that the lozenge preparation is very safe in OTC use, with or without initial advice from a pharmacist. There is no reason to suspect that the safety of the lozenge if scheduled as S2 would differ from the chewing gum.
- Inappropriate long-term use may occur, but abuse potential is low and unlikely to be higher than other forms of NRT that are scheduled in S2.
- The packaging of the lozenges has been designed to deter children from accidental misuse.
- The safety data from clinical trials and the post-marketing surveillance support a conclusion that the therapeutic index during appropriate use is wide.

The Committee noted that pre-meeting comments were received from:

- XXXXXXXXX, supported the rescheduling of nicotine lozenges to Schedule 2 like other NRT's making it easier for himself and staff to give the advice and options to help people quit smoking.
- XXXXXXXXX is of the view that rescheduling of nicotine lozenges to Schedule 2 will increase their availability to the public and provide consistency with other NRT products.
- XXXXXXXXX, supported the rescheduling of nicotine lozenges to Schedule 2 as it will increase their availability to the public and provide consistency with other NRT products. The views expressed by XXXXXXXXX are also supported.
- XXXXXXXXX, supported the rescheduling of nicotine lozenges to Schedule 2 in line with other Schedule 2 NRTs. Research indicates that quit rates through the use of nicotine lozenges are at least double and the safety profile of the lozenge is similar to other forms of NRT.

The Committee was aware that XXXXXXXXX was unable to comment due to insufficient information in the gazette notice and reserved the right to make comments pending disclosure of further information in the June 2003 NDPSC minutes.

A member informed the Committee that the indications for use met the Schedule 2 classification and since 2001 NDPSC consideration there is now good evidence of safety in normal use, with an estimated exposure of XXXXXXXXX individuals. The side effects are characterised as normal and the incidence of drug-drug interaction, based on the post-marketing experience, was of low severity. Whilst the Committee considered bioavailability was a previous concern for potential overdose in children through ingestion (93% absorbed after chewing and swallowing) the data in the UK and anecdotal data suggests this a rare occurrence. The member accepted it could be argued that whether the product is Schedule 2 or Schedule 3 is unlikely to influence the likelihood of accidental ingestion. The Member considered that the Committee's previous concerns had been addressed, that the marketing experience of nicotine lozenges had been acquired, and a Schedule 2 classification would be consistent with other NRT's.

The Committee gave additional consideration to the higher bioavailability of nicotine but agreed it was no longer an issue for retaining nicotine lozenges in Schedule 3.

DECISION 2003/38 - 24

The Committee agreed to include nicotine lozenges in Schedule 2 of the SUSDP on the basis that:

- The indication meets the criteria for Schedule 2 product.
- The overall safety profile is now reasonably well characterised and shows a low frequency of adverse events that are generally minor and similar in frequency, type and severity to those reported with other NRT products.
- There is now suitable marketing experience available, both within Australia and overseas, which indicates the spontaneous reporting of adverse events is low. Post marketing surveillance also indicated that the lozenge preparation is safe in OTC use.
- The Committee's previous concerns with the absence of clinical experience and the potential for overdose in children, given the high nicotine bioavailability, had now been allayed.

Schedule 3 – Amendment

NICOTINE – amend entry to read:

NICOTINE for use as an aid in withdrawal from tobacco smoking in preparations for sublingual use.

Schedule 2 – Amendment

NICOTINE – amend entry to read:

NICOTINE for use as an aid in withdrawal from tobacco smoking:

(a) in chewing gum;

(b) in lozenges; or

(c) in preparations for:

(i) inhalation; or

(ii) transdermal use.

14.1.4 LEVONORGESTREL

PURPOSE

The Committee considered an application seeking to reschedule levonorgestrel in a two-tablet pack, of 0.75mg per tablet, for emergency post-coital contraception from Schedule 4 to Schedule 3 of the SUSDP.

BACKGROUND

Emergency contraception (EC) includes hormonal combinations of oestrogen and progestogen and progestogen-only oral contraceptives. The combination of oestrogen and a progestogen (the Yuzpe method) is taken within 72 hours of unprotected sexual intercourse and repeated 12 hours later. The progestogen-only method consists of 0.75 mg of levonorgestrel in two doses taken in the same manner as the Yuzpe method.

The precise mode of action for hormonal EC 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 preventing implantation.

Levonorgestrel is a synthetic progestogen and is the active isomer of norgestrel. Levonorgestrel tablets for EC were included in the Australian Register of Therapeutic Goods (ARTG) on 9 October 2001, indicated for use 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 recommended dose for levonorgestrel EC is 2 tablets of 0.75mg each, 12 hours apart, within 72 hours after unprotected intercourse.

At the November 1988 NDPSC meeting levonorgestrel was included as an individual entry in Schedule 4 of the SUSDP. Prior to that date, levonorgestrel was included in the generic Schedule 4 entry for sex hormones.

DISCUSSION

Members were informed that a large number of public submissions had been received, many were after the closing date. The Committee agreed to consider the late public submission up to and including those received by the close of business on 19 June 2003. Correspondence received after the 19 June 2003 would not be considered by the NDPSC.

The Committee also agreed that people who had made submissions which were considered by the Committee, including the late submissions, would be invited to make a further public submission following the publication of gazettal notice of amendments from the June 2003 NDPSC meeting and the record of reasons for scheduling decisions.

The Committee was aware that there had been media interest in this matter and noted recent media releases [Deleted].

In 1996, the *Therapeutic Goods Act 1989* (the Act) was amended to include a definition and special requirements for 'restricted goods'. These are therapeutic goods, which are intended for use in women as abortifacients. Restricted goods may not be imported into or approved for marketing in Australia without the written approval of the Minister.

Members were informed that the issue of whether levonorgestrel was an abortifacient had been considered by the Therapeutic Goods Administration (TGA) at the time of product registration. The TGA had sought advice on whether levonorgestrel is an abortifacient which concluded that an abortion cannot occur before implantation and that EC's, such as levonorgestrel, which operates prior to implantation, are not abortifacients and not subject to the "restricted goods" provisions under the Act.

Members were reminded that when exercising its powers the Committee must take into account s52E of the Act and the relevant parts of the Australian Health Ministers Advisory Council (AHMAC) Guidelines for the NDPSC.

The Committee noted the following arguments were raised in the application to reschedule levonorgestrel for EC to Schedule 3:

- It has been used for this purpose for more than 20 years in some countries with a high efficacy and safety profile.
- In recent years it is recognised as the optimum treatment for EC on efficacy and safety grounds.
- It is available OTC in countries including UK, France, Portugal, Denmark and Sweden.
- Studies have shown that where wider availability has been introduced, the intervention of a physician has not been considered essential and that no significant safety issues have been raised.
- It has been acknowledged that abdominal pain subsequent to the use of levonorgestrel could be an indicator of ectopic pregnancy.
- It was contended that the wider availability of levonorgestrel for EC would reduce the rate of unintended pregnancies and this would flow through to reduce the number of abortions.
- Education and monitoring programs would be put in place to facilitate the introduction of the medication as OTC in Australia, and these would assist with obtaining objective data to support the benefits and safety of the wider availability.

The Committee noted the following issues raised in the report evaluating the sponsor's rescheduling application prepared for the Committee:

- Two clinical trials, the "Ho and Kwan study" and the "pivotal study" compared levonorgestrel 0.75mg to ethinyl oestradiol 100µg plus levonorgestrel 500µg (the Yuzpe method). The Ho and Kwan study allowed treatment to be initiated up to 48 hours post-intercourse whereas the pivotal study allowed a 72-hour gap between treatment initiation and intercourse. Both studies used 2 tablets, the second taken 12 hours after the first, as the proposed dose. In the Ho and Kwan, and pivotal studies respectively, the pregnancy rates were 2.9% and 1.1% with levonorgestrel treatment alone compared to 3.5% and 3.2% using the Yuzpe method. The number of observed/expected pregnancies with levonorgestrel in the Ho and Kwan study vs. pivotal study were 8/19.8 and 11/76.3, representing 60% and 86% "prevented fraction" respectively. This compared to 9/22 and 31/74.2 or 59% and 58% prevented fraction for the Ho and Kwan study vs. pivotal study respectively with the Yuzpe method. Thus, it can be appreciated that whereas the pivotal study allowed a 72 hour gap vs. 48 hour gap in the Ho and Kwan study, there was a lesser pregnancy rate with levonorgestrel in the study which allowed for more delayed treatment (2.9% for up to 48 hours treatment vs. 1.1% for up to 72 hours treatment with levonorgestrel). The sponsor state that the sooner the consumer takes the medication after unprotected sexual intercourse, the more likely it is that pregnancy will be prevented, a key argument for allowing OTC usage.
- Adverse events (AE) seen in these studies were fatigue (~17-24%), flu syndrome (1%), abdominal pain (~18%), nausea (~16-23%), vomiting (~3-6%), diarrhoea (~5%), dizziness (11-18%), headache (~17%), breast tenderness (~11-16%), increased bleeding (~14%) and vaginal haemorrhage (1-3%). These events however were similar to or even lesser in frequency than seen with the Yuzpe method. AEs did not result in any discontinuations in either study nor were ectopic pregnancies or congenital abnormalities reported.
- In a periodic safety update report (PSUR) covering 1 January 2002 to 30 June 2002, safety data was received by medical affairs of XXXXXXXXXX, from worldwide sources and sales of XXXXXXXXX tablets of levonorgestrel 0.75mg (this was estimated to indicate XXXXXXXXX uses). During this period, only 46 reports of AEs were reported. In addition, Medline, Drug Registry, Cochrane Library and ScienceDirect Databases were searched; it was stated that no serious and/or unexpected adverse reports were identified in the literature during the specified reporting period. Four ectopic pregnancies were reported from the UK during the 6 months. It was stated that the calculated frequency of ectopic pregnancies in patients using levonorgestrel was higher than that among the women who were not using emergency contraceptives. A second PSUR covering the period 1 July 2002 to 31 December 2002 was provided. During this period there were sales of XXXXXXXXX tablets of levonorgestrel 0.75mg (XXXXXXXXX uses). Forty-four reports were provided with 11 cases of unintended pregnancy, 6 ectopic pregnancies and individual cases of convulsion and congenital anomaly. In conclusion, in these 2

PSURs, with the exception of increased ectopic pregnancies, there were no new or emergent adverse events identified.

- There have also been recent literature reports of heightened ectopic pregnancy rates by Woolley and Harrison-Woolrych (J. Fam. Plann Repo. Health Care 2003; 29:5-6). These authors concluded that the risk of this occurrence outweighs the benefits of progestogen only emergency contraception, with which the evaluator agreed. Although a survey of gynaecologists supported the heightened risk of ectopic pregnancy in patients (4.1% vs. 1.1-1.8% ectopic pregnancy rate reported spontaneously; Gainer et al. Contraception 2001; 64: 17-21), post-marketing surveillance data for the commercial product in France including 7 ectopic pregnancies from an estimated total of 21,000 pregnancies suggested that this was unlikely to be higher than the spontaneous rate. There were only 2 cases of adverse reactions in the ADRAC database reported up to November 2002, of which neither was an ectopic pregnancy XXXXXXXXX.
- The sponsor stated that monitoring for public health impact would include a proposal that Medicare rebates be monitored to determine if there is a decrease in abortion rates with a wider availability of levonorgestrel as an emergency contraceptive, in addition to monitoring of ADRs by yearly reports from ADRAC. However, there have not been data provided by the sponsor that abortion rates had decreased since the original marketing of XXXXXXXXX compared to pre-availability of this agent. It was the evaluator's view that this information clearly needs to be available to quantify the public health benefit, which would bolster justification for more widespread availability. It is also proposed by the sponsor to provide appropriate training materials for pharmacies immediately prior to rescheduling of levonorgestrel. A UK guideline provided in the submission appears to be a comprehensive, appropriate and clear document including points to consider before supplying the agent.
- Although there is some concern with abuse or over-use of this method for birth control (Ellerston et al. Contraception 2000; 61: 145-186), the information provided suggests that only 20% of participants in 1 study had used emergency contraception on 2 occasions and only 6% used it 3 or more times, suggesting this may not be a problem.
- The Evaluator drew the following conclusions:

(i) Whilst it would be desirable to have levonorgestrel EC available more widely under Schedule 3, it was recommended that Schedule 3 listing be withheld at present until several important issues are resolved, as listed below in (ii) to (iv):
(ii) In terms of public health benefit of Schedule 3 availability of levonorgestrel, given its OTC availability in many countries, is there evidence available that a reduced abortion rate ensues? Moreover, is there any data available in Australia or elsewhere which demonstrates reduced abortion rates since prescription availability of XXXXXXXXX?
(iii) Given its widespread OTC availability, what is the pattern of adverse event rates since institution of OTC availability overseas. The PSURs do not seem to distinguish rates for prescription vs. OTC use.

(iv) The sponsor's central claim is that widespread and therefore earlier availability of this agent will result in lower pregnancy rates as referred to in the Ho and Kwan and pivotal studies. However, examination of the summary of the efficacy results from these 2 studies suggest that in the pivotal study, where levonorgestrel was allowed for up to 72 hours between treatment initiation and intercourse, the pregnancy rate was lower than that seen in the Ho and Kwan study in which treatment was allowed to be initiated for a shorter time, up to 48 hours post-intercourse (1.1% vs. 2.9% or 86% vs. 60% prevented fraction of pregnancies). This compared to no substantial differences seen when the comparator Yuzpe method (ethinyl oestradiol plus levonorgestrel) was used (pregnancy rates of 3.2% and 3.5%, or 58% and 59% prevented fractions for the pivotal vs. Ho and Kwan studies, respectively). The evaluator did not have available primary data from these studies, which claimed that there were lower pregnancy rates associated with shorter intervals between intercourse and drug administration, and these data should be provided.

The Committee noted the pre-meeting submissions received which are detailed at Attachment 2. The main arguments in support of the rescheduling proposal contained in public submissions were summarised as:

- It is a safe and effective emergency contraceptive option.
- Most women using EC normally use another contraceptive method but have missed pills or had a condom breakage or other problems.
- A Schedule 3 classification would provide women with a more readily available and timelier access to EC without necessarily consulting with a medical practitioner. The necessity to make a medical appointment, wait for a prescription to be issued and then obtain the medication from a pharmacist all act to delay the likelihood of the first dose being taken at the earliest time, without taking into account the costs of a medical visit.
- Published evidence appeared to support the claim for greater efficacy of levonorgestrel as emergency contraception the earlier it is taken.
- Given the number of abortions each year in Australia it is possible that many women in Australia are unaware of options for emergency contraception and it could be argued that the available option of the existing S4 availability of levonorgestrel, has been under-utilised.
- The proposed Schedule 3 classification would minimise barriers to obtaining EC and could extend the public health benefit by contributing to a reduction in the rates of unintended pregnancies and the number of abortions. However, it was acknowledged that this needed to be confirmed by valid data.
- S3 supply of levonorgestrel EC would not necessarily result in its use as a substitute for traditional contraceptive methods.
- Progestogen-only EC is available OTC in a number of countries through accredited pharmacies. In such cases, consumers are provided with information on the effectiveness, prevention and testing of sexually transmitted infections, as well as

information on contraceptive options, follow-up, and appropriate warnings against using EC as a regular form of contraception.

- Specific training for pharmacists about the provision of this information would be required to ensure that it is delivered in suitable privacy and in a manner, which does not in itself act as a barrier to requests for emergency contraception.

The main arguments opposing the rescheduling proposal contained in public submissions were summarised as:

- The risks of adverse effects such as ectopic pregnancy, venous thromboembolism, and teratogenicity might be greater in the absence of the intervention of a medically qualified prescriber.
- An established excess risk of ectopic pregnancy, as reported by the NZ Medicines Adverse Reactions Committee (MARC), the British Medical Officer and the WHO, makes this medication unsuitable for OTC use.
- The lack of long term safety data on the use of EC in Australia.
- The potential for abuse in teenagers and the potential hazards to women who repeatedly use EC. Many respondents specifically considered teenagers to be at risk of inappropriate use.
- Many respondents argued that EC is an abortifacient.
- The ongoing need for professional medical advice.
- Pharmacists are not appropriately trained to provide the necessary advice and the pharmacy setting would not provide adequate privacy for the necessary counselling.
- Appropriate consideration needs to be given to a resolution made at the 2003 UK Royal College of Nursing Congress, to support the need for regulation of assessment for emergency contraception. This resolution reiterated the matter of whether privacy and confidentiality could be given in a pharmacy environment and whether patients have sufficient information when they buy OTC EC.
- The potential public health and safety issues associated with exposure to high doses of levonorgestrel EC when compared to the mini-pill (low doses of levonorgestrel).
- Should levonorgestrel be rescheduled, advertising was not supported.

In discussing the evaluation report, a member related New Zealand's experience with the OTC use of levonorgestrel EC in preventing unplanned pregnancy. Available data in NZ shows that the rates of unplanned pregnancy and unplanned intercourse are very high, suggesting that at least half of the population does not use any form of contraception. It was pointed out that every episode of unplanned intercourse does not result in pregnancy and that it would be unrealistic to expect that the use of EC could be linked to any effect on abortion rates. Further it would be unrealistic to expect an EC-related decrease in abortion rates, given that abortion rates have been climbing since they have been measured. The member considered the side effect profile of levonorgestrel EC is better than the available alternatives.

Members noted that in NZ levonorgestrel is a prescription medicine but may be sold for EC by registered nurses or pharmacists recognised by their respective professional bodies as having competency in the field of sexual and reproductive health. By rescheduling to Schedule 3 in Australia the controls in Australia and New Zealand would be similar even though the regulatory status would be different. It was noted the labels in both countries would also be different.

Members were aware of a recent Australian media report suggesting the use of levonorgestrel EC might increase the risk of ectopic pregnancy. However, the Committee was also cognisant that the Adverse Drug Reaction Advisory Committee (ADRAC) had received only two reports of adverse drug reactions from an estimated XXXXXXXXX units sold, both involving unintended pregnancies. There have been no Australian cases of ectopic pregnancy reported to date from the S4 use of levonorgestrel EC. It was considered that ectopic pregnancy would have a high likelihood of both association with use and reporting where it had been used on prescription.

The Committee noted the NZ MARC considered 3 reports of ectopic pregnancy related to the use of levonorgestrel EC in NZ. The NZ MARC recommended that the CMI for levonorgestrel EC include appropriate warnings for ectopic pregnancy.

The Committee noted a statement issued by UK Chief Medical Officer in January 2003 indicating there had been twelve cases of ectopic pregnancy reported, out of 201 unplanned pregnancies reported to the UK Committee on the Safety of Medicines (CSM). The CSM advised women should be encouraged to seek treatment as early as possible after unprotected intercourse and advised that treatment failure may occur. Women who do not experience a normal period after use of EC should follow up to exclude pregnancy and the possibility of ectopic pregnancy should be considered, particularly in women with a previous history of ectopic pregnancy, fallopian tube surgery or pelvic inflammatory disease.

Another member mentioned the survey of gynaecologists supported the heightened risk of ectopic pregnancy in patients (4.1 % compare with 1.1 – 1.8% ectopic pregnancy rate reported spontaneously). Several members remarked that this was from a retrospective targeted survey, which may have biased the survey.

The Committee considered the prescribing information for levonorgestrel EC addressed the importance of follow up and the possibility of ectopic pregnancy. The Committee also noted the draft Consumer Medicine Information (CMI) included information advising the consumer to see a doctor in three weeks time, especially if they have not had a period by then and information relating to tubular pregnancy, and the need for regular contraception.

In considering the issue of access, lower pregnancy rates and abortion rates, the Committee noted that these issues are influenced by public education. A member questioned if there is any evidence/data to support the contention that the availability of EC could result in a reduction in unplanned pregnancies on a population basis. Whilst

the Committee acknowledged a reduction in abortion rate was desirable, it may not be easy to link it to the availability of EC through conventional epidemiological data.

The issue of ready access to effective EC is an equally important consideration. Several members maintained that levonorgestrel EC was simply another contraceptive option and it was important to expedite the timely access to women who have unprotected intercourse. Notwithstanding the lack of data to support a decrease in abortion rate the majority of members were of the view that making levonorgestrel EC more readily available to women should provide a net public health benefit.

The Committee considered that access to levonorgestrel EC as a prescribed (S4) treatment may also depend on the willingness of a medical practitioner to prescribe it. Rescheduling levonorgestrel EC to S3 would offer an opportunity for women to take more responsibility and control over their access to this substance.

The Committee accepted that, while levonorgestrel EC is not the most appropriate option for long-term contraception, it is an effective method of post-coital contraception. Moreover, the Committee considered that the issue of timely access is just as important as effectiveness in relation to the use of levonorgestrel EC.

The Committee noted the potential for serious AEs associated with levonorgestrel EC use. However, it was recognised that the potential for such AEs to occur was low based on data provided but less of a public health issue compared with AEs and social problems associated with abortion and unwanted pregnancy.

There was concern that rescheduling levonorgestrel EC may foster a more reactive approach to the use of contraception rather than a preventative approach to contraception. However a member advised there is no real evidence of such a trend with OTC use overseas, and suggested that it is more likely a theoretical argument, since it is not a cheap treatment option. It was also suggested that possible side effects, such as nausea,would act as a deterrent to routine use of EC as a regular form of contraception.

The Committee considered further whether S3 access to levonorgestrel EC would undermine the use of pro-active contraception. The submission from the XXXXXXXXX noted that the OTC availability of EC had been extensively reviewed. Studies on four continents have shown that advance provision of hormonal EC to women at risk for unintended pregnancy does not decrease traditional contraception. The Committee was unaware of any other support for the concern that normal contraceptive practices would be altered by the wider availability of levonorgestrel EC. It was noted that if women abandoned traditional contraception methods and used EC repeatedly, menstrual irregularities would be the likely result. This would presumably act as a further deterrence to women against the repeated use of EC. In a Scottish study women were randomised into groups, one given a packet of EC to keep at home and one given information about EC and where to obtain it. The study showed the use of EC in the two groups was equivalent.

The Committee acknowledged there are concerns relating to the use of levonorgestrel EC by teenagers, but considered that instructions against such use would have been addressed as part of the registration process.

During the discussion a member raised the issue of whether a pharmacist might be exposed to a legal liability in the event of a patient suffering an adverse reaction to levonorgestrel EC supplied as an S3 medicine. The members believed this potential liability would be no different to any other Schedule 3 medicine.

A member informed the Committee that experience with OTC access of levonorgestrel EC in NZ had been positive and concerns relating to its use in conjunction with sexual assaults and rape had not materialised. There had been no issues relating to privacy, and training of pharmacists had been adequate, including the provision of advice on contraception and STDs.

Members questioned the appropriateness of the pharmacy setting to discuss personal and private issues and a concern was expressed of the readiness of pharmacists to provide such personal advice. It was understood that the issue of privacy is currently being addressed by pharmacies and many are establishing private areas for counselling.

Members' attention was drawn to the XXXXXXXXX submission, which indicated that pharmacists would prefer to develop a collaborative model of primary care with general practitioners. The XXXXXXXXX initially considered that there was a need to explore this further prior to fully endorsing the rescheduling of levonorgestrel EC to S3, as well as giving more consideration to the type of information to be given at counselling. Another member advised that the pharmacists have acquired a lot of information from the United Kingdom experience with OTC availability of levonorgestrel EC. The issues raised by the evaluator had been considered and addressed during the Committee's discussion.

In considering the levonorgestrel EC rescheduling application the Committee took into account the following matters which are specified in Section 52E of the *Therapeutic Goods Act 1989*:

(a) the toxicity and safety of a substance;

The Committee noted there was a large body of overseas experience regarding the safety of levonorgestrel for EC, including OTC use. The Committee noted levonorgestrel for EC was effective and considered the safety profile appropriate for Schedule 3. It was also noted the toxicity and safety of the substance was taken into account at the time of product registration.

(b) the risks and benefits associated with the use of a substance;

The Committee accepted there were potentially significant benefits of reducing unplanned pregnancy and abortion rates through timelier access to an effective EC, when used in conjunction with professional advice from a pharmacist.

The Committee noted there are risks associated with using any medication and the potential risks associated with the use of levonorgestrel as an EC were highlighted in many public submissions, including ectopic pregnancy, thromboembolism and teratogenic effects. It was also noted that the use of levonorgestrel as an EC has been associated with minor AEs including fatigue, flu syndrome, abdominal pain, nausea, vomiting, diarrhoea, dizziness, headache, breast tenderness, increased bleeding, and vaginal haemorrhage.

The health risks associated with abortion are higher compared to the risks associated with the use of levonorgestrel EC. The Committee concluded the risk:benefit ratio to be appropriate for an S3 medicine.

(c) the potential hazards associated with the use of a substance;

The Committee noted that the proposal was associated with a commitment from the distributors to provide training materials for pharmacy including specific guidelines for onward referral to a medical practitioner. The Committee regarded this as a positive step to reduce identified hazards. The hazards were also considered in conjunction with (b) and (g).

Counselling by a pharmacist at the point of sale and appropriate information in the CMI should help educate consumers in the safe and effective use of levonorgestrel EC.

(d) the extent and patterns of use of a substance;

Whilst the NDPSC normally requires at least 2 years of local clinical use or local post-marketing experience with the substance before considering a rescheduling proposal as outlined in the AHMAC Guidelines, the NDPSC considered suitable and sufficient evidence, in lieu, was provided. This included a pattern of Schedule 4 use in Australia and comparable information from overseas countries, in particular New Zealand, where levonorgestrel is available OTC.

(e) the dosage and formulation of a substance;

The dosage proposed and presentation of the product should be appropriate for inclusion in Schedule 3.

(f) the need for access to a substance, taking into account its toxicity compared with other substances available for a similar purpose;

Access was a key issue discussed by the Committee in the rescheduling consideration. The Committee accepted the argument that rescheduling levonorgestrel EC to S3 would provide women with timely access to an effective emergency contraceptive agent. Such OTC access would reduce the likelihood of recourse to other, possibly less effective or more dangerous, options for post-coital contraception, including abortion.

(g) the potential for abuse of a substance;

The Committee gave consideration as to whether wider OTC availability would lead to a tendency for levonorgestrel to be used as a primary form of contraception and result in a more extensive use in women and teenagers. However current OTC experience in NZ and worldwide suggests this may not be the case as noted in studies from the UK supporting this conclusion. Repeated use in women and teenagers was considered unlikely, given the available data did not support the routine use of emergency contraception nor did it alter the preference to use traditional methods of contraception. The Committee noted that unpleasant minor side effects associated with levonorgestrel EC should provide an additional deterrent to abuse.

The Committee acknowledged that a number of submissions argued that levonorgestrel is in fact an abortifacient. If so, its use as an abortifacient could be considered to constitute abuse. However, the Committee accepted the validity of the TGA's advice that levonorgestrel for EC is not abortifacient, noting that levonorgestrel is intended to be taken prior to implantation and may be ineffective post implantation.

(h) the purposes for which a substance is to be used;

The Committee noted the proposed purpose of use is the same as the prescription medicine. The condition (unprotected intercourse) does not require the diagnosis or management of a medical practitioner.

(i) any other matters that the Committee considers necessary to protect public health, including the risks (whether imminent or long-term) of death, illness or injury resulting from its use; and may take into account the labelling, packaging and presentation of a substance. Australian Health Ministers' Advisory Council Guidelines for NDPSC.

The Committee also took into account the Schedule 3 AHMAC Guidelines.

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The Committee agreed to include levonorgestrel in a two tablet pack, of 0.75mg per tablet, for emergency post-coital contraception in Schedule 3 of the SUSDP taking into account s52E of the Therapeutic Goods Act 1989 and the Australian Health Ministers Advisory Council Guidelines for the NDPSC. The decision was based on the following matters:

- Enabling timely access to levonorgestrel for EC.
- A well-established safety and efficacy profile.
- Levonorgestrel for EC use has been available in several countries for a number of years including use as a product not requiring a medical practitioner's prescription.

- The purpose is considered suitable for Schedule 3 listing and the product satisfies the criteria for Schedule 3 listing.
- The distributors undertaking to provide appropriate training materials and educational materials for pharmacies.
- The pharmacist is required to provide professional advice and counselling to consumers to ensure that the product is used safely and effectively.

The Committee did not consider an Appendix H listing for levonorgestrel because there was insufficient information available at the time to make an informed decision.

Schedule 3 – New entry

LEVONORGESTREL in packs of 2 tablets each containing 0.75 mg or less of levonorgestrel for emergency post-coital contraception.

Schedule 4 – Amendment

LEVONORGESTREL – amend entry to read:

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

14.1.5 MOMETASONE

PURPOSE

The Committee considered an application seeking to reschedule mometasone for the short-term prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over, to Schedule 2. This item should be read in conjunction with Item 13.2 - Mometasone intranasal preparations for paediatric use.

BACKGROUND

Mometasone is a topical glucocorticosteroid with local anti-inflammatory properties at doses used in allergic rhinitis that are not systemically active. It undergoes extensive first-pass hepatic metabolism and has an extremely low systemic bioavailability following intranasal administration ($\leq$0.1%) and risk of systemic toxicity is low.

Mometasone in aqueous nasal spray for the short-term prophylaxis or treatment of seasonal allergic rhinitis (SAR) in adults and children 12 years and over was re-scheduled from Schedule 4 to Schedule 3 in November 1999. The October 2002 meeting agreed to extend the indication of mometasone in Schedule 3 of the SUSDP to include the short-term prophylaxis and treatment of perennial allergic rhinitis (PAR) in adults and children aged twelve years and over.

DISCUSSION

The Committee noted the XXXXXXXXX application highlighted the following:

- XXXXXXXXX is at least as safe and effective as other Schedule 2 treatments for allergic rhinitis, such as oral and topical antihistamines and sodium cromoglycate. Additionally, it allows consumers the option of a convenient, once daily dose, for the prophylaxis of seasonal allergic rhinitis.
- Allergic rhinitis is currently regarded as a condition which is appropriate for self-diagnosis as is evident from the numerous therapies already available without pharmacist supervision. Furthermore, the current scheduling of sodium cromoglycate preparations as Schedule 2, suggests that prophylactic therapy for allergic rhinitis is also able to be sufficiently managed by consumers and does not require pharmacist supervision.
- Mometasone furoate undergoes extensive first pass hepatic metabolism and has an extremely low systemic bioavailability following intranasal administration (≤ 0.1%). Therefore, there is a very low potential for systemic toxicity.
- Extensive trials assessing the efficacy and safety of mometasone furoate for the treatment of allergic rhinitis have been conducted in adults and children. They have indicated that there is no evidence of harmful effects when used for up to 12 months.
- There was no evidence of HPA-axis suppression, untoward side effects on the nasal mucosa or deleterious ocular effects following the long-term administration of intranasal mometasone in adults and adolescents (≥ 12 years).
- Intranasal mometasone has been marketed internationally since 1997 and in Australia since 1999. Safety data gathered post-marketing have not revealed any new findings or increased reporting frequency for mometasone.

The Committee noted the evaluation report stated the following:

- The evaluator accepted that mometasone aqueous nasal spray is at least as safe and effective as other S2 treatments for allergic rhinitis. Allergic rhinitis is, it is argued, currently considered a condition appropriate for self-diagnosis in the adult population. Furthermore, the current scheduling of beclomethasone for these indications under S2 suggest that prophylactic treatment for allergic rhinitis can be managed by the consumer without pharmacist supervision.
- Extensive trial and post-marketing surveillance data previously reviewed by the evaluator for the S3 application for seasonal allergic rhinitis (SAR) in adults and adolescents suggest that there is low or no evidence of harmful effects when used for up to 12 months in adults and also there is low potential for systemic toxicity or hypothalamus-pituitary-adrenal (HPA) axis suppression.
- The evaluator previously reviewed the clinical trial data set and safety profile of intranasal mometasone for the October 2002 NDPSC meeting. It can be appreciated that mometasone furoate intranasal spray is safe and effective when given once per

day in adults and adolescents >12 years for the treatment or prophylaxis of allergic rhinitis.

- There was no evidence of HPA axis suppression at standard doses in either normal subjects or in patients with allergic rhinitis receiving up to 1600µg/day for 28 days (8 times the recommended daily dose) or 400µg/day for 36 days. Furthermore, there was no evidence of HPA axis suppression following long-term administration of mometasone furoate 100-200µg/day for 12 months in adults. In addition, no significant nasal mucosal changes were seen in up to 12 months use with approved doses.
- Local adverse events (AE) in adults predominated although they were not substantially different to those seen with placebo or active comparators in the clinical trials data set.
- In the clinical trial data set in adults and adolescents >12 years of age, 3,210 patients received intranasal mometasone 50-800µg/day for allergic rhinitis. The most common AEs reported (in ≥1%) were headache, epistaxis, pharyngitis, nasal burning and irritation, rhinitis and sneezing. These were however comparable to the incidences seen in patients treated with placebo or active controls.
- There were no new or untoward adverse event profiles seen in cumulative periodic safety update reports covering 19 February 1997 to 18 September 2001 with a supplemental line listing for 19 September 2001 to 30 June 2002.
- The total number of AEs reported in Australia since the marketing of intranasal mometasone in September 1999 were provided and in adults and adolescents >12 years there were 23 AEs with XXXXXXXXX and 2 with XXXXXXXXX. The most frequently reported AEs in Australia were a decreased therapeutic effect (15%), epistaxis (15%), nasal burning/irritation (9%) and headache/migraine (8%). These are appropriately listed in the Product Information and Consumer Medicine Information documents.
- The evaluator concluded that it would be reasonable to have Schedule 2 listing for the indication of allergic rhinitis in adults and children ≥12 years.

The Committee noted that pre-meeting comment were received from:

- XXXXXXXXX - supported the proposal to reschedule mometasone and budesonide in light of the recent NDPSC decision to reschedule beclomethasone to Schedule 2. XXXXXXXXX also proposed that fluticasone be simultaneously considered for rescheduling to Schedule 2 and enclosed justification for a class switch.
- XXXXXXXXX - highlighted that long term treatment using corticosteroid can have systemic effects and believed that mometasone should only be available to the patient with consultation to a doctor or pharmacist in order to receive the appropriate dose and thereby minimise the systemic effects. Furthermore patients using mometasone over several months or longer should be examined periodically for possible changes in the nasal mucosa. XXXXXXXXX also requested the Committee consider the

potential for long-term inappropriate use of XXXXXXXXX, as the TGA approved indication is for the short-term treatment, 3 to 6 months.

The Committee agreed that the XXXXXXXXX proposal's to reschedule fluticasone would need to be the subject of a separate application for consideration at a future meeting.

The Committee acknowledged XXXXXXXXX arguments but considered they had been addressed in the evaluator's report and as such were not a serious impediment to the rescheduling proposal.

The Committee was advised that currently there are five corticosteroids, (budesonide, flunisolide, fluticasone, mometasone and triamcinolone) listed in Schedule 3 for intranasal use, for the treatment or prophylaxis of seasonal and perennial rhinitis (allergic rhinitis, AR) for up to 6 months in adults and children 12 years and over. A sixth steroid, beclomethasone was recently moved from Schedule 3 to Schedule 2 for the same uses. Of these six steroids, five are currently marketed in Australia and have been evaluated by ADEC - beclomethasone, budesonide, fluticasone, mometasone, and triamcinolone.

The Committee noted that the Medicines Evaluation Committee (MEC) considered the need for warning statements in relation to HPA axis or growth suppression for intranasal corticosteroids included in Schedule 3 at its February 2001 meeting. MEC concluded that these were not necessary given the restriction on use to adults and children aged 12 years and over.

Members were reminded that the PAR indication had been included in Schedule 3 at the October 2002 meeting. However the Committee acknowledged there are difficulties in distinguishing between SAR and PAR. It was also remarked that mometasone has a lower bioavailability relative to beclomethasone which had recently been rescheduled to Schedule 2.

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The Committee agreed to reschedule mometasone to Schedule 2, for the short-term prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over, based on:

- Extensive local and overseas experience of intranasal mometasone, which demonstrates it's effective for the treatment of allergic rhinitis;

- Allergic rhinitis does not require medical diagnosis, is readily diagnosed by the consumer, and is amenable to self-monitoring while pharmacist advice or counselling would be available if necessary;

- Available information supports the conclusion that intranasal mometasone is substantially safe in use in adults and children 12 years old and over.

Schedule 2 – New Entry

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 and when packed in a primary pack containing 200 actuations or less, for the short-term prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

Schedule 3 - Amendment

MOMETASONE – delete entry.

Schedule 4 - Amendment

MOMETASONE – amend entry to read:

MOMETASONE except when included in Schedule 2.

APPENDIX H - Amendment

Mometasone – delete entry.

14.1.6 CODEINE/PARACETAMOL

PURPOSE

The Committee considered an application seeking to amend the Schedule 3 entry for codeine to include compounded divided preparations containing codeine 11.5 mg and paracetamol 500 mg, with a recommended daily dose of 90.5 mg of codeine, in a primary pack containing 12 or less dosage units.

BACKGROUND

Codeine was listed in Schedule 2 and 4 of the SUSDP at the November 1969 NDPSC meeting. At the May 1982 NDPSC meeting the Committee amended the Schedule 3 entry for conformity with the Schedule 2 requirements. Subsequently the Committee considered the Schedule 3 entry at various meetings in relation to toxicity, confining the allowable analgesic combinations, rescheduling larger sizes of lower dose codeine products and reducing the availability of codeine preparation for illicit use. At the May 2000 NDPSC meeting the Schedule 3 entry was amended to allow a recommended daily dose of 60 mg or less of codeine as there were no safety concerns associated with this change and a need for consistency in the availability of codeine and all non-opioid analgesic combination preparations.

[Deleted]. XXXXXXXXX is currently included in the ARTG as a prescription only medicine. It contains 15 mg of codeine phosphate and 500mg paracetamol in blister

packs of 4, 10, 20 or 50 tablets and has been available in the Australian market since August 1994.

DISCUSSION

The Committee noted XXXXXXXXX requested the consideration of amending the Schedule 3 entry for codeine to accommodate XXXXXXXXX, which contains paracetamol 500mg and codeine 11.5mg (equivalent to 15mg codeine phosphate), with a limit of 12 dosage units or less per primary pack. The application raised the following points:

- The indication for XXXXXXXXX is acute pain management or short-term analgesia in patients suffering from moderate to severe pain. XXXXXXXXX is equivalent in formulation to XXXXXXXXX, which is currently available as a Schedule 4 product. The proposed dose is 2 tablets every 4-6 hours, up to a maximum of 8 tablets in 24 hours.
- There is a range of analgesics which are currently under Schedule 2 (ibuprofen, naproxen) and Schedule 3 (diclofenac), as is Nurofen Plus (a combination of ibuprofen 200mg with codeine phosphate 12.8mg), available OTC for use in the management of strong pain. XXXXXXXXX argues their adverse effects such as gastrointestinal problems limit value.
- The scheduling of the as a non-advertisable Schedule 3 product, will ensure its use requires pharmacist advice.
- Limiting the pack size to 12 tablets, ie. 1½ days maximum worth of treatment, requires the patient to seek advice of a healthcare professional if pain persists, or it can be taken for interim pain relief until medical advice can be sought eg. for dental pain or for migraine.
- XXXXXXXXX would provide, by improving access for short-term analgesic relief, a public health benefit by enabling broader access to a product (via Schedule 3 listing) for the relief of self-limiting acute moderate to severe pain without need for recourse to their GP.
- Based on industry sales data, paracetamol and codeine phosphate combinations are widely used by the healthcare professionals (for the management of moderate to severe pain) and the public (for the self-management of mild to moderate pain).
- The potential for toxicity in paracetamol overdose and potential for extraction of codeine for illicit uses are contained by the limited pack size of 12 tablets. Given this limited pack size it is argued that the potential for diversion is less than with existing Schedule 2 and Schedule 3 combinations.
- The pack size is limited to 12 tablets giving a total of 6 g of paracetamol. The product is recommended for adults and children 12 years and over. If a 12-year-old child were to ingest the entire contents it would be slightly less than an acute toxic dose. Additionally, tablets being blister packed and contained in a cardboard carton, with the ends safety sealed with tamper evident tape achieve safety. The entire carton

is over-wrapped in clear wrapping and the ends are fused to provide an additional tamper evident barrier.

The Committee noted the evaluation report concluded the following:

- A double-blind, randomised dental pain study confirmed efficacy and PSURs and ADRAC reports that reflected a low incidence of significant adverse events, it is reasonable to conclude that paracetamol 500mg / codeine phosphate 15mg is an effective treatment for short-term acute moderate to severe pain, eg. dental work or migraine headache.
- A 12 pack, as proposed under Schedule 3, would conform to Schedule 3 criteria ie, preparations for therapeutic use which are substantially safe in use but for which counselling or advice from a pharmacist is required. There is no need for medical advice and obviously pain syndromes can be identified by the consumer and verified/advised by the pharmacist, and do not require ongoing or close medical management.
- There is minimal evidence of abuse potential and in the small pack size, overdose with paracetamol or extraction and diversion of codeine phosphate is unlikely given the existing larger pack sizes of Panadeine and the lack of data for abuse potential or misuse in post-marketing data.
- There is a low risk of masking underlying conditions in short-term use and appropriate caveats of seeking medical advice should pain persist need to be included in the CMI. The 12 pack would only provide 1½ days supply; this would be consistent with the need to seek medical advice should pain not be relieved.
- The Evaluator considered this product is suitable for listing in Schedule 3.

The Committee noted public submissions were received from:

- XXXXXXXXX stated they have a Schedule 3 product and given the lack of specific information in the gazette notice wish to register an interest in this item. XXXXXXXXX also requested that the NDPSC foreshadow any revised amendments to the Schedule 3 entry so the full impact by stakeholders can be considered.
- XXXXXXXXX markets OTC medicines containing codeine and has an interest in this item. XXXXXXXXX stated there is inadequate information in the Gazette notice to consider the possible impact on labelling, packaging, presentation, extent and pattern of use, dosage and formulation, or access. XXXXXXXXX requests the right to make post-meeting comment.
- XXXXXXXXX was unable to make a comment and wished to reserve the right to make comments pending disclosure of further information in the June 2003 NDPSC minutes.
- XXXXXXXXX is a sponsor of non-prescription analgesic product and requested further details on this item. Subsequently the Secretary verbally advised XXXXXXXXX of further details of the proposal.

- XXXXXXXXX were not able to comment specifically on this item given the absence of information in the gazette notice. However, XXXXXXXXX supported uniform scheduling throughout Australia and will provide further comment after the meeting.
- XXXXXXXXX – supported an amendment to the Schedule 3 entry for codeine to include an increase in codeine to 11.5 mg, an increase in the maximum daily dose to 90.5 mg codeine and a limit of twelve dosage units per primary pack. The XXXXXXXXX does not support an Appendix H listing. The XXXXXXXXX considered this formulation would provide consumers with access to another alternative in the treatment of acute moderate to severe pain and allow pharmacists the opportunity to exercise their professional judgment in cases restricted to the temporary relief of acute moderate to severe pain states that require no more than one and a half days treatment.

The Committee acknowledged the number of public submission expressing interest in this item, seeking further information and wanting to be able to provide a post-meeting submission. The Committee noted the XXXXXXXXX supported the proposal but did not support an Appendix H listing.

The Committee was informed that the TGA Treaties and Monitoring Unit advised that the rescheduling proposal would have no implications relating to the International Drug Treaty Conventions and import/export controls under Customs legislation.

The Committee noted there are approximately 250 products, containing codeine phosphate, included in the ARTG.

The Committee appreciated that a scheduling change triggered by this application that would effectively reschedule some existing Schedule 4 products to Schedule 3 for use with pharmacist advice and represented a 10% increase in the allowable codeine content in Schedule 3 products.

The need to restrict the allowable codeine concentration in Schedule 3 to the proposed 11.5 mg dose per unit and 90.5 mg recommended daily dose in small pack sizes was considered. The Committee confirmed it does not support product specific scheduling and believed that a broader Schedule 3 entry was appropriate. The Committee agreed it was more appropriate to consider 12 mg or less of codeine per dosage unit with a recommended daily dose of 100 mg or less of codeine in a pack of 12 or less dosage units.

The Committee also considered whether to broaden the proposed Schedule 3 entry to allow other non-opiate analgesics in the entry but agreed that it was appropriate to confine the current consideration to compounded codeine preparations containing only paracetamol.

A Member questioned whether there was a need for a short-term combination codeine analgesic product to be available OTC and whether there was data to demonstrate that this treatment offered an extra benefit compared with paracetamol. It was noted that a recent study evaluated the analgesic efficacy of paracetamol 500 mg and codeine

phosphate 15 mg and showed that combination treatment was superior to single paracetamol use in post-operative dental pain (McLeod AG et al. Aus Dental J 2002; 47:147-151).

The Committee noted the applicant's proposal to retain Appendix K. It was also noted the draft label included a sedation warning statement. However Appendix K was not considered appropriate as it applies only to dispensed medicines. As a result the Committee considered whether a sedation warning in Appendix F, would be required for codeine preparations included in Schedule 3. The Committee was advised that in comparison promethazine, a sedating antihistamine, does not require an Appendix F sedation warning when included in Schedule 3 of the SUSDP. It was suggested that the Committee refer the inclusion of a label sedation warning statement to MEC for consideration at registration.

The Committee discussed the possible inclusion of codeine in Appendix H. Members were reminded that the application was for a non-advertisable Schedule 3 product and that the XXXXXXXXX submission did not support an Appendix H listing. The Committee agreed not to support an Appendix H listing as no specific proposal was submitted.

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The Committee agreed to accommodate divided preparations containing 12 mg or less of codeine compounded and paracetamol, with a recommended daily dose not exceeding 100 mg of codeine, in a primary pack containing 12 or less dosage units in Schedule 3 of the SUSDP on the grounds that:

- It is substantially safe in use but requires professional advice by a pharmacist;
- The symptoms can be easily identified by the consumer and verified by a pharmacist and do not require medical diagnosis; and
- Low potential for abuse and harm from inappropriate use.

Schedule 3 – Amendment

CODEINE – amend entry to read:

CODEINE when compounded with:

> (a) a single non-opiate analgesic substance in divided preparations containing 10 mg or less of codeine per dosage unit and with a recommended daily dose not exceeding 60 mg of codeine; or
>
> (b) paracetamol in divided preparations containing 12 mg or less of codeine per dosage unit and with a recommended

daily dose greater than 60 mg but not exceeding 100 mg of codeine when:

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

(ii) in a primary pack containing 12 or less dosage units;

except when included in Schedule 2.

14.1.7 BUDESONIDE

PURPOSE

The Committee considered an application seeking to reschedule budesonide 32 µg, in aqueous nasal spray, from Schedule 3 to S2 for the short-term prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over. This item should be read in conjunction with Item 14.1.8 – Budesonide intranasal preparations for paediatric use.

BACKGROUND

Budesonide is a non-halogenated glucocorticoid structurally related to 16-alpha-hydroxyprednisolone.

Budesonide for use in bronchial asthma and allergic rhinitis was first included in Schedule 4 in July 1990. Following the November 1998 NDPSC meeting aqueous nasal sprays containing beclomethasone, budesonide and flunisolide, indicated for seasonal allergic rhinitis (SAR) were included in Schedule 3 to harmonise scheduling with New Zealand. Budesonide was included in Appendix H at the August 2000 NDPSC meeting. At the October 2002 NDPSC meeting it was agreed to reschedule intranasal budesonide for the treatment of perennial allergic rhinitis (PAR) from Schedule 4 to S3. This decision was made on the basis of the submitted post-marketing safety data and that no safety issues were expected to arise from the short-term use of intranasal budesonide for the prophylaxis or treatment of allergic rhinitis.

The products XXXXXXXXX and XXXXXXXXX, XXXXXXXXX and XXXXXXXXX and XXXXXXXXX are included in the ARTG with XXXXXXXXX as the sponsor.

DISCUSSION

The Committee noted the XXXXXXXXX application highlighted the following:

- Well-established safety and efficacy profile in the proposed patient population
- Only intranasal corticosteroid with a category A pregnancy categorisation.

- Substantial history of safe and controlled access to the product whilst under pharmacist's supervision.
- Extensive post-marketing surveillance data showing no major concerns, including the potential for systemic effects.
- Allergic rhinitis is easily self-diagnosed and treated in adults and does not necessarily mandate pharmacist consultation.
- Intranasal budesonide is already included in appendix H of the SUSDP and in light of general requirements regarding safety and efficacy for such a product in Appendix H this would also augur in favour of de-scheduling to S2.
- A unit dose of 32 µg per dose with a maximum recommended dose of 256 µg is proposed.
- Public health benefits of down-scheduling budesonide include:

  Improving existing public awareness will indirectly improve self-diagnosis abilities.
  Increasing awareness of prophylactic treatment options lessens the need for reliever therapies.
  Increased compliance.
  Decreased need for pharmacist consultation.
  Decreased costs to society, patients and pharmacists.

- XXXXXXXXX actuation is available in 47 countries.

The Committee noted the evaluation report stated the following:

- In two periodic safety update reports covering the period 1995 to 2001, there was no evidence of overdose, drug abuse or misuse, no increased risk for mucosal atrophy after long-term nasal biopsy studies, and no reports of drug interactions, overdose, drug use or misuse. There was 1 report of pregnancy although a healthy child was delivered.
- The 2001 to 2002 PSUR revealed no worrisome or new trends of adverse events; thus, this large post-marketing exposure and established safety record would make this product suitable for S2 listing in adults/adolescents >12 years.
- It is argued that allergic rhinitis is a well recognised and identified condition which the adult consumer is able to diagnose, treat and monitor.
- The evaluator agreed that rescheduling from S3 to S2 would not impart any negative public health impact from this action, in view of the long established and broad base of efficacy and safety and low potential for excessive use or misuse. Greater access would in fact be expected to improve the management of allergic rhinitis.
- The evaluator recommended that intranasal budesonide XXXXXXXXX for the short-term (<6 months) treatment of allergic rhinitis in adults and adolescents >12 years of age be accepted for listing in Schedule 2.

The Committee noted that pre-meeting submissions were received from:

- XXXXXXXXX who supported the proposal to reschedule mometasone and budesonide in light of the recent NDPSC decision to reschedule beclomethasone to Schedule 2. XXXXXXXXX also proposed that fluticasone be simultaneously considered for rescheduling to Schedule 2 and enclosed justification for a class switch.
- XXXXXXXXX who highlighted that long term treatment using corticosteroid can have systemic effects and believed that mometasone and budesonide should only be available to the patient with consultation to a doctor or pharmacist in order to receive the appropriate dose and thereby minimise the systemic effects. Furthermore patients using mometasone or budesonide over several months or longer should be examined periodically for possible changes in the nasal mucosa. XXXXXXXXX also requested the Committee consider the potential for long-term inappropriate use of XXXXXXXXX, as the TGA approved indication is for the short-term treatment, 3 to 6 months.

The Committee agreed that the XXXXXXXXX proposal's to reschedule fluticasone would need to be the subject of a separate application for consideration at a future meeting.

The Committee acknowledged XXXXXXXXX arguments but considered they had been addressed in the evaluator's report.

A Member highlighted that budesonide has a Category A pregnancy categorisation and the considerable post marketing experience indicates low systemic side effects. It was also considered that allergic rhinitis is a condition easily self-diagnosed by the consumer.

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The Committee agreed to reschedule budesonide in aqueous nasal spray, to Schedule 2 for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over based on:

- Extensive local and overseas experience of intranasal budesonide, which demonstrates it's effective for the treatment of allergic rhinitis;
- Allergic rhinitis does not require medical diagnosis, is readily diagnosed by the consumer, and is amenable to self-monitoring while pharmacist advice or counselling would be available if necessary;
- Available information supports the conclusion that intranasal budesonide is substantially safe in use in adults and children 12 years old and over.

Schedule 2 – New Entry

BUDESONIDE in aqueous nasal sprays delivering 50 micrograms or less of budesonide per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations

or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

Schedule 3 – Amendment

BUDESONIDE – delete entry.

Schedule 4 - Amendment

BUDESONIDE – amend entry to read:

BUDESONIDE **except** when included in Schedule 2.

Appendix H - Amendment

BUDESONIDE – delete entry.

14.1.8 BUDESONIDE – PAEDIATRIC USE

PURPOSE

The Committee considered an application seeking to include budesonide for the treatment and prophylaxis of seasonal allergic rhinitis (SAR) in paediatrics aged 6-11 years, in Schedule 3 of the SUSDP. This item should be read in conjunction with Items 13.10 – Budesonide and 14.1.7 – Budesonide.

BACKGROUND

Budesonide is a non-halogenated glucocorticoid structurally related to 16-alpha-hydroxyprednisolone.

Budesonide for use in bronchial asthma and allergic rhinitis was first included in Schedule 4 in July 1990. Following the November 1998 NDPSC meeting aqueous nasal sprays containing beclomethasone, budesonide and flunisolide, indicated for seasonal allergic rhinitis (SAR) were included in Schedule 3 to harmonise scheduling with New Zealand. Budesonide was included in Appendix H at the August 2000 NDPSC meeting. The October 2002 NDPSC meeting agreed to reschedule intranasal budesonide for the treatment of perennial allergic rhinitis (PAR) from Schedule 4 to S3. This decision was made on the basis of the submitted post-marketing safety data and that no safety issues were expected to arise from the short-term use of intranasal budesonide for the prophylaxis or treatment of allergic rhinitis.

The products XXXXXXXXX and XXXXXXXXX, XXXXXXXXX and XXXXXXXXX and XXXXXXXXX are included in the ARTG with XXXXXXXXX as the sponsor.

DISCUSSION

The Committee noted the XXXXXXXXX application highlighted the following:

- The short-term management of SAR in paediatrics is suitable for an OTC classification. The symptoms are easily recognised by parents/patients. Pharmacist can also verify the diagnosis of SAR and control the ongoing short-term management of SAR.
- Paediatric patients are being denied OTC access to the full range of medications for SAR and may result in patients being treated sub-optimally with current OTC medications rather than seeking physician advice. The inclusion of paediatrics in Schedule 3 would legitimise "off-label" use and ensure appropriate warnings applicable for this group are incorporated within the labelling.
- Intranasal budesonide has a well-established safety and efficacy profile in the treatment and prevention of SAR in paediatric patients.
- Budesonide nasal sprays have been used in paediatric patients for more than 15 years. The safety and efficacy data has been reviewed and accepted by the TGA for both the initial presentations of 50 and 100μg/spray and the current lower daily dose presentations of 32 and 64 μg/spray.
- The majority of contraindications, drug interactions and precautions are the same for both the paediatric population and the current adult/adolescent OTC population and are covered in the XXXXXXXXX CMI and package insert.
- The adverse event profiles are also similar between the proposed and current Schedule 3 populations, with the majority being mild, transient and local in nature. It is acknowledged that all corticosteroids have the potential for systemic effects although intranasal corticosteroids have a lower risk compared to inhaled and oral presentations.
- The data provided concluded that there are only rare cases of either growth suppression or adrenal dysfunction associated with the use of intranasal budesonide within the proposed patient population. Similar observations have been made for adrenal dysfunction with only 2 paediatric cases being reported in over 15 years.
- The risk to patients of these systemic effects is further decreased by the restriction to short term use only (not more than 6 months) and the current Schedule 3 labelling precautions do not exceed the maximum recommended daily dose and to down titrate to the lowest effective dose. This combined with appropriate warnings with the CMI and package insert will ensure the appropriate use of the product.
- The inclusion in Schedule 3 provides public health benefits which include:
  - availability of a presentation to allow the lowest potential intranasal corticosteroid daily dose (64μg/day).
  - simplified management of SAR.

- advertising will increase the awareness in parents of the condition, types of symptoms, timing of the season, need for prevention and need to treat individual symptoms to enable optimal management of the condition.
- a reduction in doctor's visits.

The Committee noted from the evaluation report that budesonide safety in clinical trial data sets and periodic safety updates showed rare events of systemic effects of corticosteroid although the paediatric vs. adult events were not clearly discernible. The Evaluator concluded that intranasal budesonide is effective and has an acceptable safety profile in the paediatric age group for SAR. Furthermore, in the recent application for intranasal mometasone for the same indication in the paediatric age group (Item 13.2), clinical professional groups namely the XXXXXXXXX and XXXXXXXXX, suggested that initiation, assessment of other anatomical possible causes for symptoms including exclusion of relevant structural nasal lesions, advice on allergen avoidance and ongoing management and monitoring during treatment including potential for growth retardation necessarily involves direct medical care. The evaluator believed the same considerations apply in the case of intranasal budesonide for SAR in children. It was thus the evaluator's view that budesonide would be appropriately retained in Schedule 4 for the paediatric indication of SAR.

The Committee noted the pre-meeting comment from XXXXXXXXX which highlighted that long-term treatment using corticosteroid could have systemic effects. XXXXXXXXX believed that mometasone and budesonide should only be available to the patient with consultation to a doctor or pharmacist in order to receive the appropriate dose and thereby minimise the systemic effects. Furthermore patients using mometasone or budesonide over several months or longer should be examined periodically for possible changes in the nasal mucosa. XXXXXXXXX also requested the Committee consider the potential for long-term inappropriate use of XXXXXXXXX, as the TGA approved indication is for the short-term treatment, 3 to 6 months.

The Committee was informed that budesonide was not approved by ADEC for the treatment or prophylaxis of PAR in children on safety grounds but was approved for the prevention and treatment of SAR in children 6 years and above with appropriate advisory statements in relation to HPA or growth suppression included in the product information. It is currently included in Schedule 4 for use in SAR in children aged 6 – 11 years.

The Committee was also informed that beclomethasone, fluticasone and triamcinolone are approved for the treatment of AR in children under 12 years of age. Warnings relating to the risk of hypothalamic-pituitary-adrenal (HPA) axis and/or growth suppression are included in the product information for these corticosteroids. They are classified as Schedule 4 products.

The Committee noted that the Medicines Evaluation Committee (MEC) considered the proposed inclusion in Schedule 3 of budesonide for the prophylaxis and treatment of SAR in children aged 6 – 11 years at its June meeting and recommended that it is not appropriate as:

- Children should be assessed by a medical practitioner before administration of intranasal budesonide in children under 12 years to determine whether they have rhinorrhoea or AR.
- The potential for growth suppression with long-term use of intranasal budesonide is very low given the low doses that are used and the low level of compliance in children.
- On-going management of treatment by a medical practitioner is warranted.
- Differentiation between SAR or PAR, even by medical specialists, is virtually impossible.

The Committee noted that ADEC considered the use of intranasal corticosteroids in paediatrics at its April 2003 meeting. ADEC recommended that intranasal corticosteroid treatment of allergic rhinitis in children aged 3-11 years should remain in Schedule 4. ADEC also made the following recommendations:

- There is an need for an accurate initial diagnosis, particularly in pre-school aged and primary school children for the reason that nasal symptoms in these age groups are easily confused- infective, non-allergic and allergic; that perennial rhinitis is relatively more common in children than seasonal rhinitis; nasal steroids in children are almost never for short term prophylaxis of seasonal rhinitis, but are used over a much longer time period for treatment of perennial rhinitis. Initial assessment should include examination for nasal obstruction and associated atopic diseases.
- There is no data that would support the potential for growth suppression.
- The ADEC concluded that there is a need for on-going management of treatment by a medical practitioner as:-

  Perennial allergic rhinitis is relatively more common in young children, compared with seasonal rhinitis.
  Treatment with intranasal steroids is likely to be required for longer than six months.
  Associated conditions frequently occur, such as asthma and the child needs to be assessed medically as part of routine follow-up.
  Complications of PAR require medical intervention.

- Other treatment modalities, such as allergen avoidance or additional medication may be required and it would be difficult for pharmacists to select those patients who would benefit from other therapies.

The ADEC agreed that there remains a great deal of confusion about the relative incidence of seasonal and perennial rhinitis in young children, about the different approaches to and indicators for, particular treatments and the duration of therapy required. Overall ADEC had no concerns regarding the safety of intranasal corticosteroids, but did have reservation regarding adequacy of initial diagnosis and assessment.

A member highlighted that there have been rare cases of adrenal insufficiency reported in post-marketing surveillance in individuals. There are data, which indicate decreased growth of children with asthma treated with budesonide long term. However final adult height was not substantially altered or of little clinical significance. There was no data of final height studies from long-term intranasal budesonide use. With regard to post marketing surveillance there has been extensive patient exposure. The clinical trial data sets and periodic safety update reports showed rare events of systemic effects. The Committee noted that the relevant safety issues are mentioned in the product information and the consumer medicine information.

OUTCOME

The Committee agreed that intranasal budesonide for the treatment and prophylaxis of seasonal allergic rhinitis (SAR) in paediatrics aged 6-11 years be retained in Schedule 4 as there is a need for initial medical diagnosis and ongoing management of treatment by a medical professional.

14.1.9 FLUCONAZOLE

PURPOSE

The Committee considered an application seeking to reschedule oral fluconazole for the treatment of vaginal candidiasis to Schedule 3 of the SUSDP.

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 Meeting where it was included in Schedule 4 of the SUSDP. XXXXXXXXX is the sponsor of XXXXXXXXX fluconazole products marketed under the brand name XXXXXXXXX. There are both oral and injectable dosage forms within the group of products containing a range of concentrations of fluconazole.

XXXXXXXXX had requested the rescheduling of fluconazole from Schedule 4 to Schedule 3 when presented as a single oral dose of 150 mg capsule for the treatment of vaginal candidiasis when topical treatment has failed to resolve the infection.

DISCUSSION

The Committee noted the following points highlighted by the applicant in support of their proposal:

- The efficacy of the treatment of vaginal candidiasis with the administration of a single dose of 150 mg fluconazole has been established. Symptomatic benefit is generally noticed within 1 day of oral dosing with fluconazole and the infection usually clears up within 2 days of treatment. A single oral dose ensures patient compliance when compared to the daily application of topical intra-vaginal imidazole for 3-7 successive days. A survey conducted in February 2002 showed only 50% of women reported completing the full course of treatment when using topical regimens. Improved patient compliance minimises the potential for recrudescence of infection due to inadequate therapy.

- Vaginal candidiasis is a common infection in women worldwide with up to 75% of sexually active women affected at least once in their lifetime. Sufferers of a first attack usually seek advice from a doctor, but become capable of recognising the symptoms of a subsequent attack. Physical or microbiological examinations generally do not occur on subsequent attacks. Topically applied imidazole antifungal agents such as clotrimazole, econazole and miconazole have been available without prescription for 15 years in Australia, which confirms that vaginal candidiasis is suitable for OTC treatment.

- Fluconazole has a favourable safety profile. The incidence of side effects is similar between fluconazole given orally and topical antifungal, although they are qualitatively different (gastrointestinal irritation rather than local application site irritation). The adverse events reported for patients treated with a single 150 mg fluconazole dose are not common and are usually of a non-serious nature. Fluconazole does not mask the symptoms of any potential serious non-candidal infections, nor is the drug effective in their treatment. It can be reasonably expected that a patient will consult a doctor within a few days when the condition is not relieved. Fluconazole presents no abuse potential and due to the single dose formulation and packaging, overdose is unlikely. Clinical drug interactions have not been reported with single-dose use in vaginal candidiasis, although a range of drug interactions are possible with multiple doses. Advice concerning these interactions is contained in the Consumer Medicine Information (CMI) leaflet.

- To safeguard against the potential hazard of misdiagnosis, it is intended that fluconazole should only be supplied to those patients who have had a previous episode of vaginal candidiasis. These patients are aware of the symptoms of vaginal candidiasis thereby minimising the mistreatment of other more serious complaints.

The Committee noted the following points from the evaluation report of the applicant's submission:

- The sponsor argued that vaginal candidiasis has previously been determined to be suitable for OTC use and that rescheduling would bring the single-dose fluconazole product in line with the topical antimycotic products that are currently included in Schedule 3. However, the indication for topical products does not require that any other treatment should have failed prior to treatment so the comparison is therefore between first-line and second-line treatments. The evidence indicated that vaginal candidiasis that has not responded to topical antimycotic treatment is not a suitable indication for OTC treatment.

- There are many infectious and non-infectious causes of vulvovaginitis and the group of symptoms that occur with candidiasis is not specific for this condition. Gynaecological specialists (including a reference provided with the submission) have argued, that microbiological identification of the causative organism should be undertaken before treatment, even when the first condition arises. Microbiological identification would be even more important after failure of a topical antimycotic product as the chance of misdiagnosis would be much higher in this group.

- The single dose pack makes any problems from accidental overdose or ingestion by children unlikely. The efficacy of the 150 mg single oral dose of fluconazole has been shown to be similar to that of the topical antimycotic preparations and in this dosage regimen it appears to be safe, although systemic effects including angioneurotic oedema and skin rashes have been reported. As the route of administration is systemic, these effects are not unexpected.

- There is good evidence that shows that women prefer a single oral dose of medication to repeated topical applications of cream or vaginal pessaries that may lead to the inappropriate use of fluconazole as a first-line treatment, which is contrary to its registration. Furthermore, it would be difficult for pharmacists to confirm that consumers requesting fluconazole had actually undertaken local treatment first.

- While the evaluator did not support the application for the rescheduling of fluconazole from S4 to S3, the evaluator provided a comment on the proposed wording for the Schedule 3 entry and suggested that it should clarify the type of topical treatment that has failed ie "topical treatment with a drug effective against Candida" or "topical antimycotic treatment" or similar wording. The evaluator felt that this would serve to clarify the type of topical treatment that has failed.

Expert comment on the resistance potential of fluconazole was sought from XXXXXXXXX. XXXXXXXXX stated the following in his response:

- *Candida* species are an increasing cause of serious infections in hospitals and resistance to fluconazole in *Candida albicans* has been correlated with failures of therapy, but mainly in AIDS patients with oropharyngeal infection.

- In many groups of patients, use of fluconazole has resulted in colonisation, then infection with innately resistant *Candida* species eg. *Candida krusei*, *Candida glabrata*.

- The issue of resistance has not been adequately analysed to establish that it does not occur. XXXXXXXXX does not agree with the company's assessment that, to date, reports of fluconazole resistance in vaginal candidiasis are rare and he does not agree that it is unlikely to occur in the future.

- Selection of other resistant *Candida* species by the use of fluconazole is common place in hospital practice and certainly occurs in the community. Infection caused by these innately resistant strains is being reported more frequently.

- XXXXXXXXX did not support the application for the rescheduling of fluconazole from Schedule 4 to Schedule 3 on the grounds of its risk of interaction with other pharmaceutical agents and the potential for the development of resistance.

The Committee noted that the Schedule 3 use proposed by the sponsor relied on the failure of topical treatment prior to the use of oral fluconazole which positioned this product as a second-line treatment option rather than a first-line treatment option. While second-line treatments usually require consultation with a doctor 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.

A Member noted that fluconazole has a half-life in excess of 30 hours, so there is a theoretical potential that it may interact with other medicines such as diabetic medication, as diabetes can be a cause of vaginal candidiasis. Another Member stated that this was a theoretical potential only as most of the inhibition of cytochrome P450 occurs on first pass and as this is a single oral dose, it should not present a problem when used for the proposed indication. The Member also noted that although it was recommended that fluconazole should not be used in pregnancy, a single oral dose of fluconazole was listed as Pregnancy Category A.

The Committee noted that XXXXXXXXX expressed concern regarding the potential for resistance to develop with fluconazole and the risk of drug-to-drug interaction. Whilst it was acknowledged that there may a be a potential for resistance to develop with long-term chronic exposure to fluconazole, this risk was unlikely to occur with administration of a single oral dose of fluconazole and given the episodic nature of vaginal candidiasis. This contention was supported by over 10 years of post-marketing experience with single oral dose fluconazole, during which no significant reports were associated with either resistance development or drug interactions with fluconazole. Additionally, members were confident that a pharmacist is able provide appropriate advice on the potential for fluconazole to interact with other medications at the point of sale, and the Consumer

Medicine Information (CMI) and Patient Information Leaflets included advice to consult a doctor or pharmacist if taking any medicine (other than oral contraceptive).

The Committee noted that substances for vaginal use currently included in Schedule 3 such as clotrimazole, econazole and miconazole are also required to be labelled with Appendix F Warning Statement (WS) 64 "*See a doctor if no better after (Insert number of days as per approved Product Information) days*". The Committee agreed that the inclusion of an appropriate label warning statement should be referred to the MEC if fluconazole was rescheduled.

A Member acknowledged that consumers may exhibit considerable preference for an oral dose over currently available OTC topical treatments such as creams and pessaries for the treatment of vaginal candidiasis as they may have developed hypersensitivity to these agents or consider topical treatments inconvenient and unpleasant. Availability of an oral treatment in an OTC setting would provide an alternative for these individuals.

The issues raised by the evlauator had been considered and addressed during the Committee's discussion. The Committee noted that the sponsor had not provided data to support an Appendix H listing and therefore this request was not considered.

DECISION 2003/38 - 29

The Committee agreed to include fluconazole in Schedule 3 for single-dose oral preparations containing 150 mg for the treatment of vaginal candidiasis on the basis that:

- Based on available data, topical and oral preparations containing fluconazole for the treatment of vaginal candidiasis have similar safety and side effect profiles, and there were no additional or unexpected safety issues identified with oral administration of fluconazole for the said indication.
- A pharmacist is appropriately placed to provide advice on the treatment of vaginal candidiasis, of which recurring symptoms can be reliably recognised by affected consumers.
- Provides an alternative OTC option for the treatment of vaginal candidiasis which may enhance patient compliance due to the presentation of the treatment ie single-dose oral treatment compared with 3-7 successive days of topical treatment. A single dose may also reduce the potential for the development of resistance.
- Fluconazole has a low abuse potential and limiting the Schedule 3 availability of oral fluconazole to single-dose preparations only should limit the potential for harm from overdose or inappropriate use.
- The indication is amenable to short-term treatment and is capable of being monitored by the consumer.

Schedule 3 – New entry

FLUCONAZOLE in single-dose oral preparations containing 150 mg or less of fluconazole for the treatment of vaginal candidiasis.

Schedule 4 – Amendment

FLUCONAZOLE – amend entry to read:

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

14.1.10 TRICHLOROACETIC ACID

PURPOSE

The Committee considered the scheduling of trichloroacetic acid in dermal preparations.

BACKGROUND

Trichloroacetic acid (TCA) was first included in Schedule 6 of the SUSDP at the March 1972 Meeting and the alkali salts of trichloroacetic acid were included in Schedule 5 in October 1980 out of session. TCA is both caustic and astringent and is used as a 10% solution for a quick escharotic for warts and for tattoo removal. It is also widely used as a chemical face peel. There are currently no registered products on the ARTG or on PUBCRIS containing TCA.

XXXXXXXXX received a complaint regarding a treatment described as “chemobrasion” which is a form of chemical skin peeling. The applicant alledges that following application of a 20% TCA solution by an enrolled nurse, the consumer was left with excessive pigmentation, blemishes and scarring attributed to the procedure and has since undergone over 12 months of further treatment aimed at correcting this outcome. XXXXXXXXX also received a subsequent unconfirmed report that TCA was also being applied by beauty therapists. XXXXXXXXX Member referred this matter to the NDPSC with a recommendation to include trichloroacetic acid for dermal use in Schedule 4 of the SUSDP with an exemption for wart and tattoo removers.

DISCUSSION

The Committee noted that while the current scheduling of TCA provided for appropriate signal heading and cautionary information, these statements were on the immediate containers, which are not usually available to the consumer undergoing facial peel treatment. It was also outlined that facial peels were usually extemporaneous preparations mixed immediately prior to their application and were used by dermatologists, nurses and beauty therapists in concentrations up to 35%. Claims made in relation to TCA peels included: to stimulate regeneration of skin cells and collagen fibres which helps to tighten skin and decrease wrinkles; decrease lines and scars on the skin and to reverse the damage done by the sun; to 'freshen' the skin, remove some

sunspots and rough scaly patches, and reduce freckles and irregular pigmentation; and may reduce the risk of skin cancer.

Members understood that several Australian web sites advertising TCA face peels indicated that pain relief may be necessary during the procedure and some recommended a mild intravenous anaesthetic or a sedative. The Members considered that if this type of pain relief was required, then the procedure was not suitable to be performed in a beauty salon setting and would require the supervision of a medical practitioner.

The Committee recalled that the use of polyacrylamide, polylactic acid and hyaluronic acid in preparations for injection or implantation for cosmetic use were included in Schedule 4 of the SUSDP on the grounds that these products required professional examination and counselling prior to use, medical supervision of technique and procedures during use and medical monitoring of post-procedural outcomes and adverse effects. Members considered that these reasons also applied to the use of TCA as a facial peel.

A Member noted that the use of TCA by doctors and nurses is an issue of professional practice and would not be addressed by a Schedule 4 entry. However, it was recognised that inclusion of TCA for dermal use in Schedule 4 of the SUSDP would prevent beauty therapists using TCA as a face peel without the supervision of a medical practitioner.

The Committee was informed that the US Food and Drug Administration (FDA) released a statement in 1992 "warning consumers about the use of skin peelers because they can cause serious injuries, particularly when not used under the supervision of a physician".

Members were advised that the New Zealand Medicines Classification Committee (NZ MCC) considered TCA at their November 2000 and May 2001 meetings and recommended that TCA be removed from the Classification Schedule. The XXXXXXXXX did not support this action, however it did not submit evidence to support this view.

A Member reported that tattoo removal was usually performed by a medical practitioner or under medical supervision and that laser techniques were now becoming more common. The Committee agreed that the use of TCA in tattoo removal carried the potential for harm, however members agreed they would be willing to consider a cut-off to exempt preparations used for tattoo removal.

The Committee noted that the extemporaneous preparation XXXXXXXXX (1 part TCA, 6 parts salicylic acid and 2 parts glycerol) was listed in the Australian Pharmaceutical Formulary and Handbook and was used for wart removal. As this preparation is prepared and labelled for an individual patient's use and the pharmacist counsels the patient prior to dispensing the preparation, Members considered that the use of TCA for the removal of warts could be exempted from the requirements from scheduling.

OUTCOME

The Committee agreed to foreshadow the inclusion of trichloroacetic acid for dermal use, except when used for the removal of warts, in Schedule 4 of the SUSDP. The Committee also agreed to consider the inclusion of a cut-off in the proposed Schedule 4 entry to exempt TCA when used for the removal of warts and tattoos at specified concentrations, rather than exempting wart removal preparations completely, and to include this intention in the pre-October gazette notice.

FORESHADOW

Schedule 4 – New entry

TRICHLOROACETIC ACID for human dermal use **except** when in preparations containing (to be determined) per cent or less of trichloroacetic acid for the treatment of warts other than anogenital warts.

Schedule 6 – Amend entry

TRICHLOROACETIC ACID **except**:

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

(b) in human dermal preparations containing (to be determined) per cent or less of trichloroacetic acid for the treatment of warts other than anogenital warts.

14.1.11 PARACETAMOL

See item 17.1.1

14.1.12 ASPIRIN

See item 17.1.2

14.1.13 MEMANTINE

PURPOSE

The Committee considered the scheduling of the new chemical entity, memantine.

BACKGROUND

Memantine is a rapid, strongly voltage dependent, uncompetitive NMDA receptor antagonist.

[Paragraphs deleted]

Approval of registration as a therapeutic good in Australia was granted on XXXXXXXXX to XXXXXXXXX for the registration of XXXXXXXXXX containing memantine hydrochloride for use in the treatment of the symptoms of moderately severe to severe Alzheimer's disease. [Deleted]

DISCUSSION

[Paragraph deleted]

A Member informed the Committee that memantine is an old drug, which has been around for about twenty years. A recent pivotal study concluded that antiglumatergic treatment reduced the clinical deterioration in moderate to-severe-Alzheimer's disease (Reisburg B et al New England Journal of Medicine 2003; 348(14):1333-41). A recent review of seven trials from the Cochrane database indicated memantine is safe and may be useful for treating Alzheimers, vascular and mixed dementia of all severities (Areosa SA & Sheriff F Cochrane Database of Systemic Reviews 2003; (1):CD003154).

[Paragraph deleted]

The Committee noted that in New Zealand memantine is classified as a prescription medicine.

OUTCOME

The Committee agreed to foreshadow, for consideration at the October 2003 meeting, the inclusion of memantine in Schedule 4 of the SUSDP as:

- It is used to treat a medical condition that requires professional medical diagnosis, management and monitoring for side effects; and
- To harmonise with New Zealand.

FORESHADOW

Schedule 4 – New entry

MEMANTINE.

14.2 SUSDP, PART 5

14.2.1 APPENDIX H

No items considered.

15. MATTERS REFERRED BY THE AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC)

15.1 NEW SUBSTANCES

15.1.1 DEFERIPRONE

PURPOSE

The NDPSC considered the scheduling of deferiprone, a new medicine.

BACKGROUND

Deferiprone is an oral iron chelating agent.

The ADEC December 2002 meeting recommended the approval of XXXXXXXXX containing deferiprone 500 mg by XXXXXXXXX for the treatment of iron overload in patients with thalassaemia major unable to take desferrioxamine therapy.

DISCUSSION

[Paragraphs deleted]

The NDPSC noted that deferiprone was not a classified medicine in New Zealand.

DECISION 2003/38 - 30

The NDPSC agreed to include deferiprone in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

DEFERIPRONE.

15.1.2 TERIPARATIDE

PURPOSE

The NDPSC considered the scheduling of teriparatide, a new medicine.

BACKGROUND

Teriparatide is a recombinant human parathyroid preparation of XXXXXXXXXX.

The ADEC February 2003 meeting recommended the approval of XXXXXXXXX for injection by XXXXXXXXX, containing the new chemical entity teriparatide 250 µg/1

mL supplied in 3 mL cartridges to be used with a multi-dose presentation pen injection device, delivering 20 μg per activation. ADEC recommended that the indication should be for the treatment of postmenopausal osteoporosis and the treatment of primary osteoporosis in men when other agents were considered unsuitable and when there was a high risk of fractures.

DISCUSSION

[Paragraphs deleted]

The NDPSC noted that teriparatide was classified as a prescription medicine in New Zealand.

DECISION 2003/38 - 31

The NDPSC agreed to include teriparatide in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

TERIPARATIDE.

15.1.3 METHYL AMINOLEVULINATE

PURPOSE

The NDPSC considered the scheduling of methyl aminolevulinate, a new medicine.

BACKGROUND

Methyl aminolevulinate is an antineoplastic agent.

The ADEC February 2003 meeting recommended the approval of XXXXXXXXX by XXXXXXXXX containing methyl-5-aminolevulinate 160 mg/g: 2 g cream, for the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp, when other treatments were considered unsuitable.

DISCUSSION

[Paragraph deleted]

The NDPSC noted that methyl aminolevulinate was classified as a prescription medicine in New Zealand.

DECISION 2003/38 - 32

The NDPSC agreed to include methyl aminolevulinate in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

METHYL AMINOLEVULINATE.

15.1.4 VARDENAFIL

PURPOSE

The NDPSC considered the scheduling of vardenafil, a new medicine.

BACKGROUND

Vardenafil is a new phosphodiesterase (PDE) inhibitor intended for the treatment of erectile dysfunction.

The ADEC February 2003 meeting recommended the approval of the application submitted by XXXXXXXXX to register XXXXXXXXX containing vardenafil HCl trihydrate 5mg, 10mg and 20mg for the treatment of erectile dysfunction (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance). XXXXXXXXX is not indicated for use by women. [Deleted]

DISCUSSION

The Committee also noted that vardenafil was classified as a prescription medicine in New Zealand.

DECISION 2003/38 - 33

The Committee agreed to include vardenafil in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

VARDENAFIL.

15.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

No items considered.

16. OTHER MATTERS FOR CONSIDERATION

16.1 1,4-BUTANEDIOL, GAMMA AMINOBUTYRIC ACID, GAMMA BUTYROLACTONE, GAMMA HYDROXYBUTYRALDEHYDE AND RELATED ANALOGUES

PURPOSE

The Committee considered the scheduling of 1,4-butanediol and related analogues and metabolic precursors.

BACKGROUND

4-hydroxybutanoic acid (commonly referred to as gammahydroxybutanoic acid or GHB) and gamma butyrolactone (GBL) were included in Schedule 9 at the November 1996 meeting, following the initial consideration in November 1991. Initially, only GHB was listed in Schedule 9 but this entry was amended by adding "…and its salt." so not to capture other substances with legitimate uses. After advice that GBL had extensive industrial and manufacturing uses, the Schedule 9 entry for GBL was deleted at the May 1997 meeting. Further extensive discussion of control of GBL using precursor legislation and other non-scheduling controls in concert with the PACIA Code of Conduct, ensued from 1997 through 2000.

The issue of the interpretation of the GHB entry in Schedule 9 and the need for a similar entry for GBL was again reviewed in June 2002 when the Committee confirmed that the GHB entry applied only to salts of GHB and did not extend to derivatives. Furthermore, the Committee confirmed that it did not consider the control of GBL through scheduling appropriate as there was widespread legitimate commercial use of GBL and that control was through State/Territory legislation and/or other mechanisms.

NOMENCLATURE:

		Synonyms
1,4-BUTANEDIOL	IUPAC	(GBD, BD, GHBD, γ-hydroxybutanol)
4-AMINO-BUTANOIC ACID	IUPAC	(GABA, Piperidinic acid)
4-HYDROXY-BUTANOIC ACID	IUPAC	(GHB, γ-hydroxybutanoate, Sod. Oxybate)
4-HYDROXY-BUTANOIC ACID NITRILE	IUPAC	(GBN, GHBC, γ-hydroxybutyronitrile, γ-hydroxybutylcyanide)
4-HYDROXY-BUTANOIC ACID LACTONE	IUPAC	(GBL, γ-butyrolactone)
4-HYDROXYBUTANAL	IUPAC	(GHBA, γ-hydroxybutyraldehyde)
2-HYDROXYTETRAHYDROFURAN		(GHTF)
2-PYRROLIDONE	IUPAC	(2P, γ-butyrolactam)

4-HYDROXY PENTANOIC ACID*	IUPAC	(GHV, γ-hydroxyvalerate)
4-HYDROXY PENTANOIC ACID LACTONE*	IUPAC	(GVL, γ-hydroxyvalerolactone, pentanolide)

* It was not clear if these substances were in fact meant to refer to the 4-METHYL analogues of GHB and GBL which strictly speaking are not the gamma-hydroxy derivatives (which are the 5-hydroxy variants)

DISCUSSION

The XXXXXXXXX reported that the XXXXXXXXXX seized a quantity of 1,4-butanediol, which is a metabolic pre-cursor to 4-hydroxy butanoic acid (GHB or gamma hydroxy butanoic acid). It was highlighted that abuse of precursors of GHB and related analogues was an emerging health issue, and that 1,4-butanediol was suspected of being sold for use as a "drink spiking" agent. In addition, XXXXXXXXX noted the change in regulatory status of these chemicals in New Zealand and recommended their inclusion in Schedule 8 or 9, on the grounds that there were no existing registered human therapeutic uses for these substances.

The XXXXXXXXX member stated that there was no equivalent legislation to the Drugs Misuse Act in the ACT, and that it had no other mechanism of controlling drugs of abuse unless they were listed in the SUSDP. Other members also reported similar problems in their jurisdiction with regard to the control of availability of GHB and GBL.

The XXXXXXXXX, XXXXXXXXX, XXXXXXXXX and XXXXXXXXX all expressed concern over the possible adverse impact that restrictive scheduling of 1,4-butanediol and related compounds may have on legitimate industrial users. These groups generally favoured a self-regulatory approach through inclusion of these analogues where appropriate in Category 1 of the PACIA Code-of-Practice (C-O-P) for Supply Diversion into Illicit Drug Manufacture. Category 1 listed chemicals that required an End User Declaration (EUD) with each purchase and may only be sold to 'account customers' or customers that are prepared to open an account. In addition, supply of these chemicals to End Users or Distributors must be delayed for a period of not less than 24 hours.

The objective of the Code-of-Practice was to establish a common system of practice for Australia scientific suppliers and chemical manufacturers, importers and distributors to:

- Protect against the diversion of chemicals and scientific equipment into the illicit products of drugs.
- Cooperate with government and law enforcement agencies in the controlled delivery of chemicals and scientific equipment destined for use in the illicit production of drugs, where this is expected to lead to the apprehension and conviction of criminals involved in such trade or production.
- Educate and train staff and where practical end users of the precursor drug chemicals as to the issues involved and the procedures to be adopted.

XXXXXXXXX claimed there were legitimate nutritional uses for these substances and that use should not be restricted without further consultation.

Members noted that an article also appeared in The Australian newspaper on the 15 April 2003 concerning the abuse of GHB in clubs around Australia. The article noted the hospitalisation of a man in Melbourne and the death of a man in Sydney as a result of ingestion of GHB. It attributed GHB's surge in popularity to its low cost ($9 for a standard 3 mL dose) and its "soft landing" as you come down from the "high". The article also reported the use of GHB as a 'date-rape' drug.

In the United States of America (US), the National Drug Intelligence Center (Information Bulletin August 2002 US Department of Justice) noted that criminal penalties associated with gamma-hydroxybutyrate (GHB) were made more stringent and law enforcement pressure rendered GHB more difficult to obtain. However, the problem of distribution and abuse of GHB analogs remained a concern.

The Committee noted that promotions of the use of GHB analogues, as legal alternatives to GHB, were readily found on the Internet.

Uses of GHB precursors and analogues:

Precursor/Analogue	Uses
1,4-butanediol	Intermediate for polyether diols, urethanes, polyesters, plasticiser in papers and cellolosics, solvent for printing inks, agvet chemicals and coatings, cleaning agent, adhesive and pharmaceuticals
4-aminobutanoic acid	Neurotransmitter, therapeutic
4-hydroxybutanoic acid nitrile	
4-hydroxybutanoic acid lactone	Intermediate for polyether diols, urethanes, polyesters, plasticiser in papers and cellolosics, solvent for printing inks, agvet chemicals and coatings, cleaning agent, adhesive and pharmaceuticals, photochemical and surface etching, battery and electrolytic electrolyte, dye solvent
4-hydroxybutanal	
2-hydroxytetrahydrofuran	
2-pyrrolidone	

Existing control of GBH and its precursors and analogues:

Jurisdiction	Control
QLD	1,4-butanediol and related analogues – Drugs Misuse Act 1986
NSW	GHB - Drug Misuse and Trafficking Act Schedule 1 (Includes GBL) plus S2
ACT	
VIC	GBL - PACIA C-O-P Cat 1
TAS	GHB - S9; GBL - PACIA C-O-P Cat 1
NT	GBD, GBL - precursor Misuse of Drugs Act
SA	
WA	
NZ	1,4-butanediol and related analogues - NZ Misuse of Drugs Act

Members noted that some States/Territories already had appropriate controls in place through legislation and that PACIA's Code-of-Practice could also provide self-regulatory controls. It was agreed that a co-regulatory approach on this issue may be appropriate at this stage, given the range of legitimate industry uses for the compounds. However, the Committee also recognised that there was a need to promote more widely PACIA's Code-of-Practice to all relevant sectors of industry across Australia to make individual companies more aware of their obligations under the Code and ensure compliance.

OUTCOME

The Committee agreed to recommend to PACIA that the following substances be considered for inclusion in the PACIA Code-of-Conduct under Category 1:

1,4-BUTANEDIOL.
4-AMINO-BUTANOIC ACID.
4-HYDROXY-BUTANOIC ACID NITRILE.
4-HYDROXYBUTANAL.
2-HYDROXYTETRAHYDROFURAN.
2-PYRROLIDONE.
4-HYDROXY PENTANOIC ACID.
4-HYDROXY PENTANOIC ACID LACTONE.

16.2 PYRIDOXINE, PYRIDOXAL, PYRIDOXAMINE

PURPOSE

The committee considered the scheduling, warning statements and cut-off for vitamin B6. This was considered in conjunction with the recommendations from the 8th meeting of the Trans-Tasman Harmonisation Working Party (Medicines) [TTHWP(M)] on pyridoxine, Item 1.8.1.1.6.

BACKGROUND

The NDPSC considered restricting the availability of pyridoxine through early and mid 1985 following advice to the Department of Health and Ageing linking high intakes of pyridoxine with sensory neuropathy in November 1984. Recognising the data deficiencies in the toxicological profile, the NDPSC referred the issue to the NH&MRC Committee on Toxicity (COT). The evaluation report on pyridoxine, prepared by the Department, was considered at the November 1985 meeting of COT which noted that in a study using beagle dogs (Phillips et al 1978):

> "… no clinical symptoms were observed at dose levels of 50 mg/kg/day although damage to nerves could be seen microscopically. The dose level of 50 mg/kg/day is equivalent to a single dose of 3500 mg for a 70-kg person. Thus 200 mg/day would provide a safety factor of some 17 times. The existence of microscopic nerve damage would tend to lower this safety factor."

The COT concluded that:

> "In relation to scheduling, the Committee (COT) agreed that there was insufficient data to determine whether 50mg or 200mg is the most appropriate daily dose above which preparations should have more restrictive scheduling."

At the November 1985 meeting of the NDPSC, the Committee considered both the evaluation report and the COT extract on pyridoxine and agreed to exemption from scheduling for recommended daily doses above 50mg/day if the product carried a specified warning statement. Throughout this period industry requested the upper limit be set in the range 200-250mg/day. After further consultation with industry, the Committee finalised the current entry to include other compounds exhibiting Vitamin B6 activity, at the November 1996 meeting.

DISCUSSION

Members recalled that, while the Committee had previously considered the paper by Phillips et al. (1978), no particular weight had been given to that article greater than that of other information available at the time. The paper by Dalton and Dalton (1987) however, which was pivotal to the EU position on pyridoxine, had not been previously considered by the Committee.

This paper by Dalton and Dalton (1987), described possible symptoms of neuropathy in women with elevated serum pyridoxine levels, who were taking doses in the range 50-500 mg/day for PMS. Members recognised that the absence of a control group, possible introduction of bias through use of focussed questioning, possible underestimation of total vitamin B6-intake, through failure to control for intake of B6 from other multi-vitamin-supplements and the lack of neuro-physiological testing to demonstrate actual physical deficit represented important deficiencies with the study.

Conversely, the positive association of elevated serum B6-levels with symptoms, evidence of recurrence for symptoms following rechallenge and the statistically significant difference in duration of treatment in those that did develop symptoms versus those women that didn't, were considered strong positives in the weight that could be given to this study.

Members were advised that the conclusions of the three most recent international expert committees held in relation to Vitamin B6 were:

- The UK Expert Group on Vitamins and Minerals in May 2003 established a safe upper limit of 0.17 mg/kg.bw/day with no adverse affects anticipated over a lifetime exposure based on the LOAEL established in the dog study by Phillips *et al* (1978). Equivalent to 10mg/day for a 60kg adult. This review also concluded that doses of 200mg/day and above taken for long periods of time were definitely associated with reports of neuropathy.

- The EU Scientific Committee on food in November 2000 established a tolerable upper intake level of 25 mg/day based on the mean intake of 117mg/day in the study by Dalton and Dalton (1987). The same review also concluded that doses above 500mg/day were generally associated with toxicity in adults but that minor neurological symptoms may be evident at doses of 100mg/day and that "… the effects cannot be dismissed". This review also clearly enunciated the evidence for an inverse relationship between dose and duration to onset of toxicity.

- The US Standing Committee on the Scientific Evaluation of Dietary Reference Intakes through its Panel on Folates and other B group Vitamins (1999) determined a tolerable upper intake level of 100 mg/day for adults decreasing to 30mg/day for infants. This was based on a NOAEL of 200mg/day from studies in humans by Del Tredici *et al* (1985) and Bernstein & Lobitz (1988).

Members noted that the Office of Complementary Medicine had prepared a safety evaluation of pyridoxine in January 2001, which included consideration of the EC and US reviews above and the predecessor UK review (which reached similar conclusions). In addition this review included a discussion of the adverse event reports for pyridoxine (98) listed with ADRAC between 1980 and November 2000. This was considered at the February 2001 meeting of CMEC which concluded that:

> "… the current 50 mg daily dose limit (for products containing pyridoxine/pyridoxal/pyridoxamine) for the application of a label warning is scientifically justified. CMEC considers that pyridoxine-induced peripheral neuropathy remains a concern with high doses of pyridoxine, but notes that, under the current Australian regulatory requirements for pyridoxine, no significant safety problems appear to have arisen."

Members were advised that the TTHWP(M) had also recommended that there was a need for an upper limit to the daily dose (200mg/day) that could be exempted from the SUSDP

with a warning label. The attention of members was drawn to Australian promotional material recommending daily doses above 200mg/day and those registered products including injectables in multi dose vials, containing above 100mg/dose.

Members agreed that there was sufficient evidence to clearly characterise a significant risk of neuropathy at doses of 200 mg/day and above in adults. Members noted that many of the conditions, for which pyridoxine was being promoted as a treatment, included neuropathy as symptom of the condition. As neuropathy was a severe and clinically significant side effect of high or prolonged pyridoxine ingestion, the Committee agreed that the decision to use these doses of pyridoxine should only be made by a medical practitioner. Members noted that injectable forms of pyridoxine spanned from low doses associated with traditional therapeutic administration for treatment of clinical deficiency and co-administration during isoniazid treatment through to high dose multi-dose vials used by various practitioners of complementary medicine.

At the lower end of the dose spectrum, the Committee could see no new evidence to alter its earlier conclusions and agreed that the 50mg cut-off for requiring warning statements remain unchanged.

As the item had not been gazetted for consideration members agreed that the new entry be foreshadowed for consideration at the October 2003 meeting and that the remaining recommendations in relation to advising New Zealand and hand-over of warning statements from Decision 8/6 of the TTHWP(M) also be returned for consideration at the same meeting.

There was some concern over the use of high dose injectables, particularly in relation to the provision of appropriate warnings when administered by complementary medicine practitioners, however the Committee felt that the provision of additional information on this aspect be encouraged. Accordingly, the Committee directed that the gazette notice in relation to the foreshadowed amendment should draw the attention of the public to the intention of the foreshadowed amendment to place all forms of pyridoxine other than oral preparations, in Schedule 4.

OUTCOME

The Committee agreed that there was a risk of neuropathy from prolonged use of pyridoxine at doses of 200 mg/day and above in adults and supported adoption of this level as the upper limit for exemption from Schedule 4.

FORESHADOW

Schedule 4 - Amendment

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE - amend entry to read:

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE for human therapeutic use **except:**

(a) in oral preparations containing 200mg or less but more than 50mg of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose when labelled with the warning statement:

WARNING - this medication may be dangerous when used in large amounts or for a long time; or

WARNING - this product contains [*insert pyridoxine, pyridoxal or pyridoxamine as applicable*] which may be dangerous when used in large amounts or for a long time; or

(b) in oral preparations containing 50 mg or less of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose.

(B) TO RECOMMEND THAT THE NZ MOH ADOPT A SIMILAR REGULATORY OUTCOME; AND

(C) THAT AT THE OCTOBER 2004 MEETING OF NDPSC FOLLOWING TRANSFER OF WARNING STATEMENTS TO THE TGA "*Required Advisory Statements for Therapeutic Goods*", THE NDPSC FORESHADOWS AMENDING ITS SCHEDULE 4 ENTRY FOR PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE TO READ:

Schedule 4 - amendment (Foreshadowed for October 2004)

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE - amend entry to read:

PYRIDOXINE, PYRIDOXAL OR PYRIDOXAMINE for human therapeutic use **except** in oral preparations containing 200mg or less of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose.

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17. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

17.1 REVIEW OF NON-PRESCRIPTION ANALGESICS

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of proposed warning statements for over the counter (OTC) analgesics for inclusion in Appendix F of the SUSDP. This item includes discussion of Items 14.1.11 – Paracetamol, 14.1.12 - Aspirin, 17.1.1 – Paracetamol, 17.1.2 – Aspirin, 17.1.3 – Ibuprofen, 17.1.4 – Naproxen, 17.1.5 – Mefenamic acid. In additional this item should be read in conjunction with Items 1.8.1.4 - Aspirin OTC and 1.8.1.5 – Paracetamol.

BACKGROUND

A Review of non-prescription analgesics, prepared by David Newgreen in February 1998, made a series of recommendations to address health and safety concerns regarding OTC analgesics, which related to matters within the NDPSC's terms of reference. Recommendations from the Newgreen Report relevant to the NDPSC were 4.4, 6.1.1, 6.1.2, 6.1.3, 6.2, 6.4, 6.5, 6.7, 6.8, 6.9, and 6.10. The May 2000 NDPSC meeting considered the Newgreen Report and the TGA's response.

In February 2003, the TGA published the *Review of Non-prescription Analgesics an Update* as a "draft for comment". This document was finalised by the MEC in April 2003 and referred to the NDPSC for consideration of the recommended changes to the SUSDP Appendix F warning statements for OTC analgesics.

DISCUSSION

The NDPSC members were provided with a copy of the *Review of non-prescription analgesic – An update,* April 2003 (April 2003 Update). The Committee noted four of

the recommendations of the April 2003 Update (numbers 9, 10, 11 and 13) and three of the Newgreen Report recommendations (numbers 6.5, 6.7 and 6.8) relate to labelling requirements for analgesics that are required by the SUSDP.

The Committee was cognizant that the responsibility for regulating label-warning statements is to be transferred from the NDPSC to the TGA in July 2005, and that MEC had asked the NDPSC to implement OTC analgesic warning statement changes in the interim.

The Committee noted there had been public submissions received from the following.

- XXXXXXXXX
- XXXXXXXXX
- XXXXXXXXX
- XXXXXXXXX
- XXXXXXXXX
- XXXXXXXXX
- XXXXXXXXX
- XXXXXXXXX

In addition the Committee noted XXXXXXXXX made an additional comment in regards to ibuprofen, conveying their concerns of duplication or proliferation of warning statements in the Australian Regulatory Guidelines for OTC medicines (ARGOM) and the SUSDP. Subsequently the OTC Medicines Section advised the NDPSC that they can be assured that the final ARGOM will be fully consistent with the warning statements MEC has proposed for Appendix F of the SUSDP.

The Committee noted the TGA and XXXXXXXXX had issued a media release on 'Guidelines for safe use of paracetamol released' and an accompanying, 'Fact Sheet – Paracetamol.' The fact sheet is to inform consumers about the safe use of paracetamol. In addition, NSW Health also distributed a Circular 2003/26 on 'Paracetamol Use' to be read in conjunction with Circular 2000/88 'Introduction of the Australian Standard Vaccination Schedule'. It provided guidance for health professionals in the use of paracetamol.

The Committee was provided with a copy of the XXXXXXXXX booklet *NSAIDS, coxibs & aspirin for inflammatory and other connective tissue disorders* (2003).

Members were informed that these public submissions, along with comments from the TGA OTC Medicines Section, were subsequently forwarded to the MEC for further consideration. The MEC considered these submissions at its June meeting and provided comments on the issues raised which is at Attachment 3. The Committee noted that in light of the public submissions received by the NDPSC, the MEC revised the proposed wording of the Appendix F warning statements, which are at Attachment 4.

A member pointed out that the public had not had the opportunity to comment on the revised wording recommended by the June 2003 MEC meeting. Furthermore, this member highlighted that the revised Appendix F warning statements proposed by the MEC may be different to those which may arise from the performance based labelling project to be included in the new therapeutic goods labelling order, which is expected to come into effect in July 2004. It was then argued there is a need to ensure that the analgesic warning statements included in Appendix F were the same as those statements to be included in the new labelling order.

This member proposed that the way forward would be for a small working group to be formed, in conjunction with the XXXXXXXXX Labelling Committee, to develop agreed analgesic warning statements as a priority.

The Committee agreed that it would not be able to resolve this issue at this meeting and accordingly considered it appropriate to refer the revised changes back to the MEC to enable it to undertake consultation with industry and provide a unified response to the NDPSC. The issue of lead-time for the implementation of warning statements was also considered a matter for MEC to resolve. A final response could then be gazetted for consideration at the October 2003 meeting.

OUTCOME

The Committee agreed to refer the revised package of warning statements for over the counter (OTC) analgesics for inclusion in Appendix F of the SUSDP to MEC and recommend that industry be consulted further with a view to providing agreed statements to the NDPSC for consideration at the October 2003 meeting.

18. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

18.1 SELENIUM

PURPOSE

The Committee considered the New Zealand Medicines Classification Committee's (NZ MCC) proposal to reschedule selenium to Schedule 2 for external medicines containing more than 2.5% selenium.

BACKGROUND

Selenium sulfide has antifungal and antiseborrhoeic properties and is used as a 2.5% and a 1% shampoo for the treatment of dandruff (pityriasis capitis) and seborrhoeic dermatitis of the scalp. It is also used as a 2.5% lotion in the treatment of pityriasis versicolor. Selenium is an essential trace element and is an integral part of the enzyme system glutathione peroxidase protecting intracellular structures against oxidative damage. Overdosage of selenium has been associated with loss of hair, nail changes, diarrhoea,

dermatitis, garlic odour of breath, fatigue, and peripheral neuropathy. Selenium sulfide has a different toxicity profile to selenium, although it can be highly toxic when ingested. Only traces of selenium sulfide are absorbed through intact skin, but prolonged use on broken skin has resulted in systemic toxicity.

The toxicity of selenium sulfide shampoos when ingested by children was discussed at the April 1994 NDPSC meeting. The Committee concluded that the hazard associated with ingestion of the 1% solution was comparable to the 2.5% solution. The volume of the 2.5% selenium solution needed to cause death in a 20 kg child is approx. 98 mL, however selenium sulfide is an emetic and most of the solution would be likely to be expelled through vomiting. The volume remaining in the child's stomach after vomiting was estimated to be 12.5 mg/kg which is below the single oral LD_{50} for the rat which is 78-120 mg/kg.

The February 2001 NDPSC meeting considered Trans-Tasman Harmonisation Working Party's (TTHWP) Recommendation 36/7 advising the NDPSC to recommend that the NZ MCC shift preparations for external use containing above 2.5% selenium from Part III to Part I. This recommendation was made on the basis that prolonged use on broken skin has resulted in systemic toxicity. The NDPSC endorsed Recommendation 36/7 and referred the matter to NZ MCC for consideration.

The May 2002 NZ MCC meeting considered the TTHWP 36/7 however the NZ MCC did not support the recommendation. The basis of the New Zealand decision was that it would make the scheduling of external products more restrictive compared to internal products, as internal products containing more than 150 micrograms per recommended daily dose would remain Pharmacy-Only. Selenium products are currently classified as General Sale or Pharmacy-Only in New Zealand ie there is no prescription category for selenium. As a result, the NZ MCC recommended that the classification of selenium for external use remain unchanged and that the NDPSC consider harmonising with the NZ classification for selenium in external preparations.

The October 2002 NDPSC meeting considered the recommendation from the NZ MCC and agreed to gazette selenium for consideration at the February 2003 NDPSC meeting. At the February meeting, the Committee noted that the origin of the current topical selenium entry was unknown and agreed to defer the item to the June 2003 NDPSC meeting to allow the history and reasons for this entry to be collated and presented to the Committee.

DISCUSSION

The Committee noted the pre-meeting submission received from XXXXXXXXX. XXXXXXXXX declared its interest in this item and reserved the right to comment further once it became apparent what was being proposed.

Members were advised that the NZ MCC's argument for not adopting Recommendation 36/7 was based on the fact that harmonising with Australia would create a Prescription-

Only classification for selenium for external use in New Zealand, when there is no existing prescription entry for selenium for internal use in New Zealand.

The Committee noted that there had been 5 cases of non-life threatening adverse reactions recorded since 1983 including contact dermatitis, headache, rash and skin discolouration. There were seven anti-dandruff hair shampoos listed on the ARTG with concentrations ranging from 5 mg/mL (0.5%) to 25 mg/mL (2.5%) selenium sulfide which are indicated for the control and prevention of itching and dandruff and for the control of seborrheic dermatitis of the scalp. All seven products were exempt from scheduling. There were 5 products listed on PUBCRIS containing up to 1% selenium sulfide with indications relating to skin conditions of cats, dogs and horses such as seborrhoea, dry eczema and non-specific dermatoses. Four of the products were exempt from scheduling while one product was Schedule 6 due to other ingredients. There were no Schedule 4 topical shampoos containing selenium sulfide listed on the ARTG or on PUBCRIS.

A library internet search produced no evidence of poisoning through the use of selenium shampoos, however the Committee noted that Martindale included a case of systemic toxicity in a woman with excoriated eruptions on her scalp following the use of a shampoo containing selenium 2-3 times weekly for 8 weeks. The woman developed a range of symptoms consistent with selenium poisoning which subsided 10 days after withdrawal of the shampoo. Toxicity data concerning the topical absorption of selenium at levels above 2.5% could not be identified. Similarly, the NZ MCC was unable to provide any toxicology data on selenium in topical preparations.

Research into the history of the selenium entry produced little data and the cut-off level to exempt for topical preparations of 2.5% of selenium sulfide appeared to originate from the historical use of anti-dandruff shampoos at that level. Due to the low level of adverse reactions reported and the non-serious nature of those reactions compared with the wide application of these products, the Committee considered the 2.5% cut-off to exempt was appropriate.

It was identified that the current cut-off to exempt in Australia for topical preparations was set at 2.5% of selenium sulfide while in New Zealand it was set at 2.5% of selenium. It was noted that in order to harmonise on the cut-off to exempt, Australia would need to raise the cut-off to 3.5% of selenium sulfide or New Zealand would need to lower the limit to 1.8% selenium to create a harmonised outcome.

Members agreed that the salt needed to be specified in the schedule entry to ensure that only selenium sulfide and not selenium selenite was used in topical products.

DECISION 2003/38 - 34

The Committee agreed to harmonise with New Zealand and reschedule selenium for human topical therapeutic use in preparations containing over 3.5% selenium sulfide to Schedule 2.

Schedule 2 - New Entry

SELENIUM in preparations for human topical therapeutic use **except** in preparations containing 3.5 per cent or less of selenium sulfide.

Schedule 4 – Amendment

SELENIUM - amend entry to read:

SELENIUM for therapeutic use **except**:

(a) when included in Schedule 2, 3, 6 or 7;

(b) in preparations for human oral use where the sum of the organic selenium expressed in micrograms and half the inorganic selenium expressed in micrograms, contained in the recommended daily dose of the preparation, does not exceed 26 micrograms;

(c) in preparations for human topical use containing 3.5 per cent or less of selenium sulfide.

(d) for the treatment of animals:

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

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

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

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

18.2 SOLANACEOUS PLANTS AND ALKALOIDS

PURPOSE

The Committee considered the New Zealand Medicines Classification Committee's (NZ MCC) recommendation to increase the cut-off for exemption in Appendix G of the SUSDP for atropine, hyoscine and hyoscyamine to harmonise with NZ.

BACKGROUND

The May 1992 NDPSC Meeting considered the proposed cut-off's for Appendix G. It was recommended that the assessment criteria of scheduling exemption be based on the principle that no more than the maximum therapeutic dose for a 10 kg child be in 1000 mL of the desired homeopathic strength. This was seen to give a toxicologically acceptable safety factor of 100 x on the basis that a child may swallow 10 mL. The cut-off for atropine was set at 100 micrograms per kg or litre and the cut-off's for hyoscine and hyoscyamine were set at 10 micrograms per kg or litre. Minor amendments were made to Appendix G at the August 1992 Meeting before being forwarded to the Public Health Committee for ratification. Appendix G was first published in SUSDP No. 8 – effective 24 December 1993.

The November 2002 NZ MCC Meeting considered a submission from XXXXXXXXX proposing to raise the cut-offs from scheduling requirements for dilute preparations of solanaceous alkaloids on the grounds that they were too low for the plant alkaloids. XXXXXXXXX proposal has been based on the principle where herbal medicines containing one hundredth of the minimum lethal dose of solanaceous alkaloids per pack can be sold as "general sale". The MCC considered this approach appropriate from a safety perspective and agreed that raising the cut-off for exemption to 300 mcg per litre or per kilo for atropine, hyoscine and hyoscyamine in 'general sale' homeopathic preparations still provides a 100-fold safety factor. The MCC also noted that the existing inconsistency in the NZ Schedules, where the cut-offs for exemption apply to both the plant material and its alkaloids, were being amended to express these cut-offs in terms of the total alkaloid content.

The February 2003 NDPSC Meeting noted that the cut-off's proposed by XXXXXXXXX were either too high or too low, depending on how they were applied. 10 mg/kg if applied to the alkaloid was too high, while 10 mg/kg of the herb was too low. The Committee agreed to defer solanaceous alkaloids to the June 2003 Meeting to allow gazettal of the consideration.

DISCUSSION

The Committee was informed that XXXXXXXXX submission to the NZ MCC outlined the active principle levels, toxic levels and therapeutic levels with regards to solanaceous alkaloids with the proposed cut-off's based on 1/100 of the minimum lethal dose. The references submitted by XXXXXXXXX concerning toxic doses related to atropine only. Fatal doses of atropine were reported at as low as 1.6 mg and as high as 100 mg in children. If atropine was at a concentration of 300 micrograms per litre, a child would need to consume a quantity in excess of 5 litres to reach the fatal dose of 1.6 mg, while an adult would need to consume considerably more. The submission stated that XXXXXXXXX supplied their products in both 30 mL and 100 mL pack sizes. If the concentration of these products were 300 micrograms of atropine per litre, over 50 bottles of the 100 mL pack size would need to be consumed with the number increasing to over 160 bottles for the 30 mL pack size to reach the fatal dose for a child of 1.6 mg. The

proposed Appendix G cut-off to exempt of 300 micrograms of atropine would allow for the maximum SUSDP listed Schedule 2 oral dose in one litre of preparation.

XXXXXXXXX stated in their pre-meeting submission that the current cut-off's for solanaceous alkaloids were appropriate and allow for dilute preparations of herbal substances such as belladonna and hyoscyamus which have been used by herbalists safely for a very long time. The XXXXXXXXX also stated that it was opposed to any tightening of the current restrictions.

The February 1992 NDPSC Meeting was of the view that if a homeopathic/low concentration preparation did not present a hazard because of its dilution, then there was no need for the requirements of scheduling to apply.

The Committee noted that as homeopathic/low concentration preparations are generally given on a repetitive basis rather than as a single acute dose, it may not be appropriate to base safe levels on acute toxicity data, but rather on the lowest effective dose level. The Committee noted the following justification which was presented in support of the existing Appendix G entry for atropine (100 micrograms/L):

An XXXXXXXXX company, XXXXXXXXX, had recommended an atropine sulfate dose of 400 micrograms for adults and 10 micrograms/kg for children to prevent drooling in cerebral palsy patients. As dry mouth can be one of the first signs of a therapeutic effect, 10 micrograms/kg may be taken as the lowest effective dose. A 10-fold factor is then applied to reach the no effect level (1 microgram/kg), and then a further 10-fold safety factor is applied to allow for individual variation of an estimated safe dose (0.1 microgram/kg in children). This would equate to 1 microgram for a 10 kg child and assuming that this is in a "standard swallow" of 10 mL, then the maximum safe concentration would be 100 micrograms/L.

The Committee did not agree with the approach outlined above and considered XXXXXXXXX rationale, which supported the maximum SUSDP listed Schedule 2 oral dose in one litre of preparation or 300 micrograms/L, to be an appropriate cut-off for atropine in Appendix G of the SUSDP.

It was noted that the current cut-off's for atropine, hyoscine and hyoscyamine in Appendix G do not reflect the relative potencies of atropine and hyoscine and hyoscyamine. Members noted that Martindale reported hyoscyamine as having twice the antimuscarinic potency of atropine and that hyoscine was a more powerful suppressant of salivation than atropine. Given the increased potency of hyoscyamine and hyoscine, the Committee based the cut-off's for these substances on a level that is half that of the cut-off for atropine or 150 micrograms/L.

The Committee noted that mother tinctures sold to homeopathic practitioners were still subject to the requirements of scheduling, however if they were diluted into smaller concentrations when they were dispensed to patients, they would be exempt if the levels were below the cut-off's listed in Appendix G of the SUSDP.

DECISION 2003/38 - 35

The Committee agreed to amend the cut-off in Appendix G of the SUSDP for atropine to harmonise with New Zealand. However, it was agreed to amend the cut-off's for hyoscine and hyoscyamine at half that of atropine based on their increased toxicity relative to atropine.

Appendix G – Amendments

ATROPINE – amend to read:

ATROPINE	300 micrograms

HYOSCINE – amend to read:

HYOSCINE	150 micrograms

HYOSCYAMINE – amend to read:

HYOSCYAMINE	150 micrograms

22. AMENDMENTS TO THE SUSDP

22.1 EDITORIAL CHANGES AND ERRATA

PURPOSE

The Committee considered various editorial changes and errata to the SUSDP.

BACKGROUND

During the consolidation of SUSDP No.17, some inconsistencies and editorial errors were discovered. These were referred back to the Committee for consideration to ensure the intent of the entry remained unchanged and to confirm that the changes had no regulatory impact. Two of the proposed changes required to be gazetted prior to the implementation of the change and needed to be foreshadowed for consideration at the next meeting.

DISCUSSION

The Committee agreed to amend the entries to provide consistency within the SUSDP and to reflect the original intent of the Committee at the time that the entries were created.

OUTCOME

The Committee agreed to foreshadow the changes to the Appendix C entry for silicone and the Schedule 7 entry for carbon tetrachloride.

FORESHADOWED

APPENDIX C – AMENDMENT

SILICONES – amend to read:

SILICONES for tissue augmentation by injection or implantation.

SCHEDULE 7 – AMENDMENT

CARBON TETRACHLORIDE – amend to read:

CARBON TETRACHLORIDE **except** in chlorinated rubber based paint containing 1 per cent or less of carbon tetrachloride.

DECISION 2003/38 - 36

The Committee agreed to adopt the editorial changes that have no regulatory impact and do not require gazettal and include them in SUSDP No.18 Amendment 2 as an errata. These changes are listed below. The Committee also agreed to include copper compounds in the cross-reference for copper-chrome-arsenic in the index of the SUSDP and to order the Schedule entries alphabetically in SUSDP No.19, consistent with International methods of indexing (eg N-octyl bicycloheptene dicarboximide in Schedule 5 will appear under "O" instead of "N").

ERRATA

SCHEDULE 2 – AMENDMENT

ACETYLCYSTEINE – correct to read:

ACETYLCYSTEINE in preparations for oral use **except** when labelled with a recommended daily dose of 1 g or less of acetylcysteine.

SCHEDULE 4 - AMENDMENTS

PHOLCODINE – correct to read:

PHOLCODINE **except** when included in Schedule 2:

(a) in divided preparations containing 100 mg or less of pholcodine per dosage unit; or

(b) in undivided preparations containing 2.5 per cent or less of pholcodine.

PYRIDOXINE, PYRIDOXAL or PYRIDOXAMINE – correct to read:

PYRIDOXINE, PYRIDOXAL or PYRIDOXAMINE in preparations for human use containing more than the equivalent of 50 mg of pyridoxine per recommended daily dose **except** when labelled with the warning statement:

WARNING - this medication may be dangerous when used in large amounts or for a long time; or

WARNING - this product contains [*insert pyridoxine, pyridoxal or pyridoxamine as applicable*] which may be dangerous when used in large amounts or for a long time.

SCHEDULE 5 – AMENDMENTS

HYDROGEN PEROXIDE – correct to read:

HYDROGEN PEROXIDE (excluding its salts and derivatives):

(a) in hair dye preparations containing 12 per cent or less of hydrogen peroxide **except** in hair dyes containing 6 per cent or less of hydrogen peroxide; or

(b) in other preparations containing 6 per cent (20 volume) or less of hydrogen peroxide **except** in preparations containing 3 per cent (10 volume) or less of hydrogen peroxide.

METALAXYL – correct to read:

METALAXYL in preparations containing 35 per cent or less of metalaxyl.

NITRIC ACID – correct to read:

NITRIC ACID (excluding its salts and derivatives) in preparations containing 10 per cent or less of nitric acid (HNO_3) **except** in preparations containing 0.5 per cent or less of nitric acid.

POTASSIUM SULPHIDE – correct to read:

POTASSIUM SULFIDE in preparations for metal treatment in containers each containing 50 g or less of potassium sulfide.

SCHEDULE 6 – AMENDMENTS

ALPHA-CYPERMETHRIN – correct to read:

ALPHA-CYPERMETHRIN

(a) in aqueous preparations containing 25 per cent or less of alpha-cypermethrin; or

(b) in other preparations containing 10 per cent or less of alpha-cypermethrin,

except when included in Schedule 5.

DIMETHYL SULFOXIDE – correct to read:

DIMETHYL SULFOXIDE

(a) when not for therapeutic use; or

(b) for the treatment of animals:

(i) when combined with no other therapeutic substance(s);

(ii) in liquid preparations containing copper salicylate and 1 per cent or less of methyl salicylate as the only other therapeutic substances; or

(iii) in clay poultices containing 2 per cent or less of dimethyl sulfoxide.

GLYCERYL THIOGLYCOLLATE – correct to read:

GLYCERYL THIOGLYCOLLATE in hair waving preparations **except** when labelled with directions for use that include the statement:

"Wear protective gloves when using. Keep out of eyes".

HYDROGEN PEROXIDE – correct to read:

HYDROGEN PEROXIDE (excluding its salts and derivatives) **except**:

(a) when included in Schedule 5;

(b) in hair dye preparations containing 6 per cent or less of hydrogen peroxide; or

(c) in other preparations containing 3 per cent (10 volume) or less of hydrogen peroxide.

PHENYLENEDIAMINES – correct to read:

PHENYLENEDIAMINES and alkylated phenylenediamines not elsewhere specified in these Schedules:

(a) in preparations packed and labelled for photographic purposes;

(b) in preparations packed and labelled for testing water **except** tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool"; or

(c) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements:

"KEEP OUT OF REACH OF CHILDREN", and

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

written in letters not less than 1.5 mm in height.

TOLUENEDIAMINE – correct to read:

TOLUENEDIAMINE in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements:

"KEEP OUT OF REACH OF CHILDREN", and

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

written in letters not less than 1.5 mm in height.

SCHEDULE 7 – AMENDMENT

SELENIUM – correct to read:

SELENIUM **except**:

(a) when included in Schedule 6;

(b) as selenium arsenide in photocopier drums;

(c) in preparations for therapeutic use other than:

(i) drench concentrates containing 2.5 per cent or less of selenium; or

(ii) pour-on preparations containing 0.5 per cent or less of selenium;

(d) in paints or tinters containing 0.1 per cent or less of selenium calculated on the non-volatile content of the paint or tinter; or

(e) in fertilisers containing 200 g/tonne or less of selenium.

APPENDIX F - AMENDMENTS

	WARNING STATEMENTS	**SAFETY DIRECTIONS**
Potassium sulphide – correct to read:		
Potassium sulfide	2	1,4
Silver salts – correct to read:		
Silver in smoking deterrents	42	

APPENDIX G – AMENDMENT

STROPHANTHUS – correct to read:

STROPHANTHUS spp.	1 mg

24. ATTACHMENTS

ATTACHMENT 1 - IBUPROFEN PUBLIC SUBMISSIONS – ITEM 14.1.2

- XXXXXXXXX – supported the proposal to exempt ibuprofen 200 mg provided appropriate warnings appeared on the product labelling.
- XXXXXXXXX – supported the proposal as it will bring Australia into line with other major countries and also allow consumers access to a drug whose safety profile in the XXXXXXXXX opinion, continues to demonstrate benefits over alternative products such as aspirin and paracetamol. XXXXXXXXX provided remarks on recent publications addressing gastrointestinal side effects, drug interaction and cardio-protective effects of aspirin. An XXXXXXXXX media release of 14 February 2003, an XXXXXXXXX Newsletter of April 2003 and the XXXXXXXXX Proceedings of the International Ibuprofen Conference held April 2002, were also provided.
- XXXXXXXXX – believed that people with arthritis benefit from having a pharmacist available to ask questions when they purchase ibuprofen from a chemist and this situation should not change.
- XXXXXXXXX – recommended the current scheduling of ibuprofen remain unchanged as there is a potential risk of adverse effects when ibuprofen is used in patients with certain disease states, or concurrently with some medications. The current scheduling for ibuprofen allows consumers access to this medicine with the safeguard of pharmacist advice.
- XXXXXXXXX – did not support the proposal as professional advice is important given there are a number of patient groups who should not take this medicine and are at risk of potential adverse effects. There is no opportunity for professional advice if the sale of ibuprofen is allowed in non-pharmacy outlets.
- XXXXXXXXX – did not support the proposal based on ibuprofen's toxicity. It can cause adverse effects when taken in modest doses in a small proportion of people with exquisite sensitivity.
- XXXXXXXXX, – believed that there are potential risks of serious drug interactions associated with ibuprofen and supplied a publication on the effect of ibuprofen on cardioprotective effect of aspirin (T M MacDonald, L Wei Lancet 2003;361:573-74).
- XXXXXXXXX – did not support the proposal. The contraindications and precautions associated with ibuprofen are such that up to 23 per cent of the Australian adult population should not use this product without some form of consultation with a healthcare professional. Clinical evidence also demonstrated additional risks, such as the role of ibuprofen in limiting cardio-protective effect of low-dose aspirin. XXXXXXXXX believed that prior to choosing an ibuprofen-containing OTC product, all consumers should be in a position to seek the advice of a healthcare professional.
- XXXXXXXXX – regarded ibuprofen as a Schedule 2 substance based on scheduling criteria. Safety issues concerning drug interactions and contraindications for

ibuprofen were outlined. Published studies and recent adverse reaction reports have also highlighted the risks associated with the use of NSAIDS together with ACE inhibitors and/or diuretics (the triple whammy).

- XXXXXXXXX – recommended the appropriate schedule for ibuprofen 200 mg is Schedule 2 and contended that the deliberations of the appropriateness of open sale of ibuprofen is not about gastrointestinal safety of ibuprofen relative to aspirin and paracetamol. The XXXXXXXXX contended that the potential impact on the health of Australian consumers from a quality use of medicine principle perspective must be considered. Examples of pharmacists' interventions in patients with certain diseases or conditions and possible medicines interacting were illustrated. The public health risk associated with the use of ibuprofen outweighs any public benefit of deregulated access and pharmacist play an essential role in decreasing this risk due to controllable factors.

The Committee took note that XXXXXXXXX had put forward that they are unable to make comment due to lack of information in the gazettal notice and wish to reserve the right to make comment pending the disclosure of further information in the minutes of the June 2003 NDPSC meeting.

ATTACHMENT 2 – LEVONORGESTREL PUBLIC SUBMISSIONS – ITEM 14.1.4

- XXXXXXXXX – supported the rescheduling proposal and referred to the reasons set out by XXXXXXXXX.
- XXXXXXXXX – submitted that XXXXXXXXX should not be available at all, as there is insufficient data available as to long-term consequences of the use of XXXXXXXXX. If made available it should be only on prescription because of family concerns, the event of a child not being able to disclose information to her general practitioner, pharmacies are considered not to be the proper place to provide advice in relation to the use, use may disguise sexual assaults and pharmacists are exposed to potential legal liability.
- XXXXXXXXX - argued that levonorgestrel, marketed as XXXXXXXXX, should not be taken off the prescription-only schedule. XXXXXXXXX contended that making levonorgestrel more easily accessible would lead to some women using the drug more regularly and outlined warning statements from WHO. The importance of requiring a doctor's prescription ensured the opportunity for a doctor to consider the woman's medical history and to do a medical examination before making a judgement to prescribe levonorgestrel was raised. XXXXXXXXX also considered that pharmacists are not the appropriate advisers to take over a doctor's responsibility. XXXXXXXXX expressed the view that the embryo is prevented from implanting in the uterine wall, causing an abortion, is hidden from consumers.
- XXXXXXXXX - are opposed to the rescheduling proposal. Current XXXXXXXXX policy supported the availability of prepacked emergency hormonal contraception (EHC), provided that medical practitioners remain sole prescribers of EHC product and that prescriptive medication is not extended to pharmacists or nurses in Australia.
- XXXXXXXXX – believed that rescheduling levonorgestrel to Schedule 3 will provide easier access for women which would increase the likelihood of levonorgestrel being effective and contribute to a reduction in unintended pregnancies and abortions. Results from an UK trial suggested EC is likely to be used an emergency back up when other methods of contraception fail or are not used. Australian studies indicated that EC is currently under-utilised in Australia due to lack of awareness about, and accessibility of, the medication. XXXXXXXXX stated there is no evidence that levonorgestrel will damage an unborn foetus if a woman uses it while already pregnant. Intentional or unintentional overdose of levonorgestrel has also been shown not to cause serious harm. It is argued that there is no evidence to suggest that access to EC lead women to favour it over use of the pill or barrier methods of contraception. XXXXXXXXX disregarded the contention that EC is an abortifacient. XXXXXXXXX consider EC supplements other forms of contraception and does not replace them.
- XXXXXXXXX – opposed the rescheduling proposal because of the potential risks associated with the use of levonorgestrel in large doses as an EC. The respondent considered pharmacists are not in a position to provide the necessary advice on issues including the potential risks and longer-term method of contraception. The

respondent contended that little is known with certainty about the extent to which the various risks, such as venous thromboembolism, and contraindications for the regular contraceptive pill apply to the taking of levonorgestrel in high, but irregular, doses. The teratogenic effects on a foetus in the event of XXXXXXXXX failing to prevent or terminate a pregnancy are unknown. The respondent regarded XXXXXXXXX as having an abortifacient effect (Kahlenborn C, Stanford JB and Larimore W The Annals of Pharmacotherapy 2002;36:465-470). The potential for abuse in teenagers was also raised. The Committee was asked to consider the UK Royal College of Nursing recent resolution to support the need for regulation of assessment for emergency contraception as it was questioned whether privacy and confidentiality could be given in a pharmacy environment and whether patients have sufficient information when they buy OTC EC. The respondent was also opposed to the advertising of this product should it be rescheduled.

- XXXXXXXXX - supported the rescheduling proposal. The WHO publication, *Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use,* has classified the levonorgestrel EC regimen as a generally benign medication which can be dispensed to women in most circumstances by health care professionals and requiring only limited clinical judgment. However all providers of EC should receive training. XXXXXXXXX stated that levonorgestrel emergency contraception has no documented medical contraindications and will not disrupt an existing pregnancy and have no teratogenic effects on the foetus or the woman. It is postulated that improving access to EC could a have significant impact on reducing the rates of unplanned pregnancies. Research in the UK and other countries demonstrated that when EC is more readily available to women it is more likely to be utilised in the case of unprotected sexual intercourse or contraceptive failure. Research also demonstrated that improved availability and usage of EC does not increase the likelihood of women to engage in unprotected sex or for women to substitute emergency contraception in the place of ongoing methods.
- XXXXXXXXX – supported the rescheduling proposal, as removing the requirement to obtain a prescription for EC would overcome a barrier in the current health system. XXXXXXXXX also supported the proposal to advertise the product.
- XXXXXXXXX – stated that levonorgestrel has an abortifacient action and raises questions about the safety of levonorgestrel compared with contraindications for the mini pill, and the medico-legal implications. Questions were also raised as to the safeguards to prevent women taking XXXXXXXXX on a regular basis.
- XXXXXXXXX – supported the proposal as it will contribute to a decrease in unplanned pregnancies and abortions and improve consumer access to EC.
- XXXXXXXXX – stated that levonorgestrel XXXXXXXXX should not be rescheduled to Schedule 3. It was argued that XXXXXXXXX is an abortifacient medication and cannot be described as safe because its main use is to destroy a human being. The psychological adverse effects of abortion were discussed. Teenagers are considered to be at risk for inappropriate use. The potential teratogenic effect and potential side effects of XXXXXXXXX compared with fifty tablets of levonorgestrel 30 mcg was highlighted. References to VACTERAL syndrome were also included.

- XXXXXXXXX – subsequently advised they have obtained legal advice which suggested the TGA could be sued for damages in respect of a decision to schedule a substance, namely XXXXXXXXX, if it was approved as an OTC pharmacist only medicine. The question of liability of an agency in the performance of a statutory function was raised concerning three issues; breach of common law duty of care, breach of statutory duty and careless performance of a statutory duty. The respondent debated the teratogenic effect of XXXXXXXXX and contrasted the potential side effects for women using the mini-pill in comparison with XXXXXXXXX. The respondent believed the medico-legal responsibility would shift if levonorgestrel were rescheduled. It was also argued that there was no safeguard to prevent women from using XXXXXXXXX as their main form of contraception.
- XXXXXXXXX – supported the proposal, believing pharmacists are in an excellent position to provide more timely access to EC, which is crucial to the effectiveness of this medication, without compromising patient safety. XXXXXXXXX proposed that it be made Schedule 3, with a stipulation that it be supplied only by pharmacists having been accredited to do so, following successful completion of an approved training course as a safety measure. XXXXXXXXX stated that XXXXXXXXX has proven to be a valuable and effective post-coital contraceptive and it is logical to make XXXXXXXXX readily available from pharmacists who are highly trained and well qualified. The overseas experience with OTC EC has also been positive. XXXXXXXXX argued that more readily available EC would reduce the incidence of abortions.
- XXXXXXXXX – summarised the role of emergency contraception as outlined by the WHO and stated that the XXXXXXXXX and the XXXXXXXXX have issued supporting statements relating to EC. Access through pharmacists in the community setting is seen as a significant advantage and the established safety profile of this medicine has assisted in facilitating the availability through various models overseas. The XXXXXXXXX, in collaboration with the XXXXXXXXX, is drafting a protocol for the supply of EC in Australia as an OTC product and developing education and training module for pharmacists. XXXXXXXXX opposed Appendix H listing as they consider product specific advertising is not appropriate and a broader public health and community education campaign would be more appropriate. There is also no information in relation to use of levonorgestrel as a non-prescription medicine in Australia.
- XXXXXXXXX – supported in principle the rescheduling proposal but did not support inclusion in Appendix H of the SUSDP. Whilst the XXXXXXXXX is aware that pharmacist supply EC OTC in several countries, they would like to ensure that pharmacists have the opportunity to undertake professional training about the supply of EC. The XXXXXXXXX would prefer to develop a collaborative model of primary care with general practitioners and would prefer to explore this further prior to fully endorsing the deregulation of EC. In addition, the XXXXXXXXX had concerns about the professional indemnity impact of Schedule 3 supply of EC.
- XXXXXXXXX – submitted a copy of their policy on EC and recommended

  - the rescheduling of levonorgestrel to Schedule 3;

- the inclusion of levonorgestrel in Appendix H;
- that consumer medicines information be available to women; and
- that pharmacists and nurse practitioners have additional training or education to dispense it effectively.

The need for greater access to EC was argued and such readily available OTC access would assist, rural and remote Australian women, and women in low socio-demographic areas. Whilst XXXXXXXXX accepted that pharmacists already have the ability to responsibly dispense EC, they also believed specific education and training is required. XXXXXXXXX submission addressed common concerns about the use of EC in relation to STD, increased promiscuity and stated it is not an abortifacient.

- XXXXXXXXX – is opposed to the rescheduling application and any promotion or easy availability of any abortifacient agents, which it considers XXXXXXXXX to be. The issue of providing information over the counter was also raised. It was contended that teenagers may resort to the use of XXXXXXXXX which is "not recommended for children" and questions of applying an age restriction and the medico-legal ramifications were asked.
- XXXXXXXXX – raised questions of how a pharmacist can control EC usage and assess any harm caused by it and contended sales assistant will sell it in a busy pharmacy. The respondent believed that young women will be expected to be more sexually available because of the ease of availability and raised concerns of the long-term effects to women's health. Further questions relating to early abortions were also raised.
- XXXXXXXXX - supported the rescheduling of levonorgestrel emergency contraception to Schedule 3, subject to the provision of appropriate accompanying information about ongoing contraception and prevention of sexually transmitted infections, on the basis that the risks are minimal and that some unintended pregnancies and pregnancy terminations are likely to prevented by these means. XXXXXXXXX also believed that levonorgestrel 0.75mg (2-tablet pack) for emergency contraception met the NDPSC guidelines for Schedule 3 substances.
- XXXXXXXXX – supported the rescheduling proposal on the basis that it is critical for the consumer to access XXXXXXXXX as soon as possible after unprotected sexual intercourse. Rescheduling this medication would make it more readily accessible to consumers in a timely manner. XXXXXXXXX availability as an OTC in countries such as UK, France, Portugal, Denmark, Sweden and some USA states has shown it does not lead to use as a routine method of contraception. XXXXXXXXX are also committed to the provision of appropriate educational materials for pharmacy.
- XXXXXXXXX – supported the rescheduling proposal in the context of the XXXXXXXXX position statement on EC, with regard for the need of a well-planned public and health professional awareness campaign that incorporates the principles of promoting protection from sexually transmitted infections and use of efficacious

methods of contraception. XXXXXXXXX contended there have been no definite serious side effects associate with levonorgestrel used as an EC though there has been attention in the literature relating to the risk of ectopic pregnancy and risk to the foetus if pregnancy occurs. XXXXXXXXX believed OTC access, with a public awareness campaign, has the potential to overcome existing barrier issues. It was argued that the increased availability of levonorgestrel as an OTC overseas has not been associated with any significant medical problems. Studies showed women were unlikely to use EC repeatedly and were likely to start regular contraception for the first time after use of EC. OTC availability has the potential to reduce unplanned pregnancy and broaden additional health professionals' involvement in women's sexual and reproductive health.

- XXXXXXXXX – supported the rescheduling proposal as there is evidence to suggest that it is more effective in preventing pregnancy after unprotected intercourse the sooner it is taken and by having it available from a pharmacist will improve timely access. The respondent considered a very detailed information sheet was essential if XXXXXXXXX is made available OTC.
- XXXXXXXXX – supported the rescheduling proposal, as it would provide improved and more equitable access to a wider range of women. It would also relieve the mounting clinical burden on primary and sexual health care services. Ideally the package should include information on testing for sexually transmitted infections, safer sex and contraceptive options.
- XXXXXXXXX - supported the rescheduling proposal on the grounds that EC works more effectively when taken as early as possible. The present system of most general practitioners working on an appointment system may mean delays and some general practitioners will not prescribe EC. The respondent considered that OTC availability also required the provision of an information sheet.
- XXXXXXXXX – supported the rescheduling proposal and the inclusion of levonorgestrel for EC in Appendix H of the SUSDP based on ample international experience to indicate that OTC access to this form of EC is effective, safe and affordable; and that pharmacists have shown themselves to be competent and responsible in the ways S3 medicines are managed.
- XXXXXXXXX – supported endeavours directed towards decreasing rate of unintended pregnancy and termination of pregnancy and views the rescheduling of levonorgestrel as a positive step. The respondent believed that XXXXXXXXX should be provided information, which emphasises that it is not intended to be used as an ongoing contraception and follow up and provides information about testing for and protection against sexually transmitted infections. Recent reviews have summarised that case for and against the supply of EC without prescription (Grimes DA N.Engl J Med 2002;347:846-9, Grimes DA & Raymond EG Ann Intern Med 2002;137:180-189, and Penney G, Brechin S and de Souza A.J Fam Plann Reprod Health Care 2003;29:9-15). These reviews concluded that the prescription requirement for EC jeopardises women's health by decreasing or delaying use of this safe, effective prophylaxis. XXXXXXXXX noted that pharmacy supply would improve prompter access to EC and likely reduce the incidence of requests for

pregnancy termination. XXXXXXXXX have stated there is a low potential for abuse or harm from inappropriate use, low incidence of severe side effects or side effects requiring medical intervention and minimal contraindications or drug interactions.

- XXXXXXXXX – opposed the rescheduling proposal for the safety of women. XXXXXXXXX stated the morning after pill is an abortifacient.
- XXXXXXXXX – opposed the rescheduling proposal on the grounds XXXXXXXXX is an abortifacient.
- XXXXXXXXX - opposed making XXXXXXXXX OTC.
- XXXXXXXXX – is concerned that the morning after pill may be sold OTC whilst the contraceptive pill needs a prescription.
- XXXXXXXXX – was concerned of the risks of ectopic pregnancy, as reported by the WHO. There would also be no means of monitoring the health of users, unlike the contraceptive pill and potential serious side effects especially if XXXXXXXXX was used frequently.
- XXXXXXXXX –raised concerns about ectopic pregnancies, which, if not monitored by medical people, can lead to risk to life and health and increased public health costs. The respondent expressed the view that the readily availability of contraceptives and abortion techniques encourages the promiscuous lifestyle.
- XXXXXXXXX – opposed the rescheduling application on the basis it requires medical advice about its abortifacient action.
- XXXXXXXXX – opposed the rescheduling proposal, and considered that a visit to the GP should not be ruled out. The Committee was asked to consider the long-term effects if the drug is abused, as there is limited data on the potential health risks.
- XXXXXXXXX – felt that the rescheduling proposal is unnecessary and unacceptable and considered XXXXXXXXX to be an abortifacient. Questions on ethical and moral ground were raised for consideration.
- XXXXXXXXX – argued that if XXXXXXXXX were more freely available, it would have the effect of encouraging more recreational sex amongst teenagers.
- XXXXXXXXX – forwarded and email from XXXXXXXXXX, stating the morning after pill is an abortifacient and opposing the change of schedule. A summary of XXXXXXXXX, submission to the NDPSC was also provided.
- XXXXXXXXX – opposed the rescheduling proposal as there is a greater risk of ectopic pregnancy as detailed by NZ MARC, the WHO and British Chief Medical Officer. The respondent considered levonorgestrel should not be dispensed without medical supervision and therefore a prescription. It was argued that the potential risks associated with teenage pregnancies also needed to be considered.
- XXXXXXXXX – was against the proposal due to possible side effects including an increased risk of ectopic pregnancy as reported by the WHO and BMO and thrombosis. The respondent referred to the Breast Cancer Prevention Institute web

site and provided a summary of the factors that increased and decreased breast cancer risk as evidence that the first pregnancy should never be aborted.

- XXXXXXXXX - opposed the rescheduling proposal because of the potential adverse risks associated with the use of levonorgestrel as an EC. A report by Kahlenborn et al stated there is a "potential for negative psychological impact on women who value human life from conception onwards and… later learn of the potential postfertilization effects." There is also a potential for abuse in teenagers and people resort to the regular use of XXXXXXXXX.
- XXXXXXXXX – did not think XXXXXXXXX should become OTC because there is a risk of ectopic pregnancy, venous thromboembolism and is opposed that people are told XXXXXXXXX is contraception and not a type of abortion.
- XXXXXXXXX – would regret the decision to reschedule XXXXXXXXX to OTC as some people may use the product whose moral convictions do not let them use abortifacient contraception. The respondent argued that such pills also increase the chances of a promiscuous attitude where the consequences of their actions are thought of after intercourse.
- XXXXXXXXX – opposed the rescheduling proposal because of the possible increased risk of ectopic pregnancy, adverse side effects as reported by Kahlenborn et al and the potential for abuse in teenagers.
- XXXXXXXXX - opposed the rescheduling application, due to the risk of ectopic pregnancy and OTC sales will not allow doctors to monitor the risks. The risk of venous thromboembolism and possible teratogenic effect was also mentioned. The respondent was also opposed because young people are told XXXXXXXXX is contraception and not a type of abortion.
- XXXXXXXXX – opposed the rescheduling proposal because of the possible link to ectopic pregnancy and regarded the pharmacy counter as the improper place to discuss implications relating to the use nor does it provide privacy. The respondent mentioned some people may not be aware that levonorgestrel has an abortifacient effect, which could cause psychological distress and trauma to those who value human life from conception. The potential for abuse by young girls and women who repeatedly use the product was also raised.
- XXXXXXXXX – are opposed to the rescheduling proposal based on the potential for abuse in uninformed women, particularly teenagers and also considered it to have an abortifacient effect. It was argued that doctors should be involved in monitoring and managing associated risks not pharmacists.
- XXXXXXXXX – opposed the rescheduling proposal due to links with ectopic pregnancy and venous thromboembolism and feared XXXXXXXXX is being promoted as a contraceptive rather than an abortive.
- XXXXXXXXX – objected to the rescheduling proposal on moral and ethical grounds and cited XXXXXXXXX submission.
- XXXXXXXXX – opposed the rescheduling of XXXXXXXXX.

- XXXXXXXXX - opposed the rescheduling application, as there is a risk of ectopic pregnancy, venous thromboembolism and possible teratogenic effect. It was argued that OTC sales would not allow doctors to monitor potential risks. The respondent was also opposed because young people are told XXXXXXXXX is a type of contraception and not an abortion. An email from XXXXXXXXX was also forwarded which had a proforma letter to the NDPSC attached.
- XXXXXXXXX – are opposed to the rescheduling proposal due to potential adverse effects, the lack of adequate risk data, the potential hazards of use and the potential for abuse.
- XXXXXXXXX – believed that XXXXXXXXX should not be sold OTC and argued its is an abortifacient. The long-term psychological effects of terminating a pregnancy were raised, as the respondent believed consumers could not be given adequate counselling in a pharmacy setting. The possible long-term effect is not known and the issue of repeated use causing possible adverse effects such as carcinomas and thromboembolic conditions was mentioned.
- XXXXXXXXX – stated that XXXXXXXXX without prescription would be a huge backward step for the health of women in Australia especially for teenage girls. The respondent raised concerns over the teratogenic effect of XXXXXXXXX and the potential side effects for women compared with the mini-pill. The likely increase in sexual activity, the potential for repeated use and the lack of safeguard to prevent women from using the morning after pill as their main form of contraception was also raised. The respondent believed the medico-legal responsibility would shift if levonorgestrel were rescheduled.
- XXXXXXXXX – believed making XXXXXXXXX OTC would be a disaster as it can cause serious health problem in teenage girls who will most likely use it as an abortifacient and contended it is best to leave it as a prescription only medicine. It was argued that doctors could also give advice and help with any follow up treatment, not pharmacists.
- XXXXXXXXX – opposed the rescheduling application due to the risk of ectopic pregnancy and OTC availability will not allow doctors to monitor levonorgestrel. The respondent also considered levonorgestrel is an abortifacient.
- XXXXXXXXX – protested to the sale of the morning after pill OTC considering it can cause an early abortion, and the risk of ectopic pregnancy and the long term effects are unknown.
- XXXXXXXXX – expressed his concern to have XXXXXXXXX sold OTC by pharmacists and argued it would cause early abortions if it were taken after fertilisation occurs. The woman involved will have no idea whether or not she has become pregnant and if it is used regularly a woman could have multiple early abortions. Early warnings about the risks have been referred to the XXXXXXXXXX, XXXXXXXXXX and the WHO. It was also argued it would be irresponsible when the damage to women's health and subsequent children are unknown.

- XXXXXXXXX – stated the push to have XXXXXXXXX available OTC by pharmacists is wrong due to the unknown long-term effects on women and subsequent offspring. The respondent contended it is an abortifacient and it is misleading to promote it as an EC. Further as reported by the WHO, there is an increased risk of ectopic pregnancy by the use of XXXXXXXXX.
- XXXXXXXXX - are opposed to the rescheduling proposal based on the published reports showing that levonorgestrel increases the risk of ectopic pregnancy; the argument that XXXXXXXXX is an abortifacient and the possible psychological impact on women, that pharmacists are not in a position to warn users not to use EC as long term contraceptive; and the possible adverse effects.
- XXXXXXXXX – was in favour of keeping XXXXXXXXX off the Schedule 4 (?3) list and was concerned that chemists are not aware of the potential effects to young people such as thromboembolism, ectopic pregnancy and teratogenic effects. The respondent was also not in favour of rescheduling, as young women will be told it is a form of contraception, not a type of abortion.
- XXXXXXXXX - opposed the rescheduling proposal due to the potential hazards of levonorgestrel as an EC, it's abortifacient effect, the lack of adequate risk data and the potential for abuse. The respondent was concerned that women who use levonorgestrel as an EC should be professionally monitored by a medical practitioner and also advised to consider a longer term method of contraception if they present for repeated use.
- XXXXXXXXX – was opposed to the rescheduling proposal due to potential risks of ectopic pregnancy, venous thromboembolism and teratogenic effects and considered XXXXXXXXX is a type of abortion.
- XXXXXXXXX – opposed the rescheduling proposal because of the potential adverse risks associated with the use of levonorgestrel as an EC.
- XXXXXXXXX – opposed the rescheduling application, as there is a risk of ectopic pregnancy and venous thromboembolism. It was argued that OTC sales would not allow doctors to monitor potential risks. The respondent was also opposed that people are told XXXXXXXXX is contraception and not a type of abortion.
- XXXXXXXXX – urged the rejection of the proposal and objected on the grounds that XXXXXXXXX is an abortifacient and women will therefore not be given the choice of informed consent.
- XXXXXXXXX – was concerned that, what is effectively an abortion pill, is being considered for OTC availability and raised questions about misuse and how information will be disseminated to pregnant women.
- XXXXXXXXX – appealed to stop any attempts to sell XXXXXXXXX OTC as the effects of this medication are not fully known and the manufacturer can not guarantee a healthy pregnancy if the women takes this medicine when the embryo has implanted. The respondent also mentioned the XXXXXXXXX.

- XXXXXXXXX – opposed the rescheduling proposal due to potential adverse health risks associated with the use of XXXXXXXXX and believed doctors need to follow up potential risks. They also considered XXXXXXXXX is misrepresented as a contraceptive due to its abortifacient effects. It was argued that there is a potential for abuse as Pharmacists are not in a position to advise women, who present for repeat courses of XXXXXXXXX, to consider a long term method of contraception and teenagers may also resort to the regular use.
- XXXXXXXXX – opposed the rescheduling proposal on the grounds it acts to end an "in existence" pregnancy, based on embryology definitions and the view that levonorgestrel is an abortifacient. Objections raised included the associated risk of levonorgestrel with ectopic pregnancies, the potential to increase the risk of blood clots in susceptible women, the potential drug interactions such as warfarin, the potential carcinogenic effect, the potential for abuse in females masking acts of sexual abuse, assault or incest. Legal and practical issues were also raised.
- XXXXXXXXX – was concerned about the rescheduling proposal as XXXXXXXXX functions as a type of abortion. The Committee was asked to consider the long-term side effects.

ATTACHMENT 3 – REVIEW OF NON-PRESCRIPTION ANALGESICS PUBLIC SUBMISSIONS – ITEM 17.1

PARACETAMOL

Keep to the recommended dose. Don't take this medicine for longer than a few days [48 hours for children and adolescents] at a time unless advised to by a doctor.

Responses received	Comments
Amend statement relating to adults to *"Do not take this medicine for longer than 5 days"* [XXXXXXXXX]	No justification was provided for specifying five days (however, consumer interpretation of *"a few days"* is also unclear).
Amend *"Keep to the recommended dose"* to the stronger statement, *"Do not take more than the recommended dose"* [XXXXXXXXX]	The originally proposed statement is positive and therefore preferred to the negative one proposed.
Confusion as to whether entire statement is proposed for all paracetamol products, or whether variations could be used for specific target audiences (2nd sentence: *"Don't take this medicine for longer than a few days at a time unless advised to by a doctor"* for adults; and *"Don't give this medicine for longer than a 48 hours at a time unless advised to by a doctor"* for paediatric use) [XXXXXXXXX]	The words in brackets are intended as an alternative for children's preparations. To avoid possible confusion the statements could be separated: Adults: *Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.* Children and adolescents: *Keep to the recommended dose. Don't give this medicine for longer than 48 hours at a time unless advised to by a doctor.*

If an overdose is taken or suspected, ring the Poisons Information Centre (131 126) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

Responses received	**Comments**
Objections raised to referring to 'overdose' on labels, as this may encourage the use of paracetamol in suicides and/or may deter people from using paracetamol, and encourage increased inappropriate use of other OTC analgesics [XXXXXXXXX, XXXXXXXXX] XXXXXXXXX considered that the reference to 'overdose' on labels is not warranted as >99.5% of OTC paracetamol users use it within the recommended daily dose. XXXXXXXXX considers paracetamol is being treated unfairly compared with other OTC medicines. If these statements are applied to paracetamol, they should be applied to all OTC analgesics to avoid potential adverse public health impact of consumers concluding that the overdose risk with OTC aspirin and NSAIDs is insignificant.	The proposed statement is based on the recommendations of the MEC's *Review of non-prescription analgesics – An update*, and was recommended because paracetamol overdose is different, in that it can result in asymptomatic, delayed, potentially fatal liver damage, whereas overdoses with aspirin and other NSAIDs do not have this delayed effect.
Concerns over inclusion of the word *"serious"* in this statement (as this may equally apply to adverse effects with other analgesics – eg. aspirin-induced asthma, use of NSAIDs during pregnancy) [XXXXXXXXX]	*"Serious"* seems appropriate here, given that fatalities have occurred following liver damage from paracetamol overdose.
XXXXXXXXX suggested that references to 'overdose' should be replaced by 'prolonged or excessive use', ie.: *Immediate medical advice should be sought in the event of prolonged or excessive use, even if you feel well, because of the risk of delayed, serious liver damage*; or *In the event of prolonged or excessive use, ring the Poisons Information Centre (131126) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.*	The problem being addressed by this warning statement is acute overdosage with paracetamol. The issue or prolonged or excessive usage are addressed by the previous warning statement (above).
Should also include NZ PIC number [XXXXXXXXX]	Agreed

Responses received	Comments
Concerns whether Poisons Information Centres have the resources to cope with the likely increase in calls if PIC phone number was included on labels [XXXXXXXXX, XXXXXXXXX, XXXXXXXXX]	The statement only advises people to contact the PIC if an overdose is taken. If overdoses are as frequent as the comments suggest, the public can only benefit from this advice.

Don't take with other paracetamol-containing products, unless advised to by a doctor or pharmacist

Responses received	Comments
XXXXXXXXX suggested *"Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist"* may be easier to read.	The SUSDP allows sponsors to vary the actual words provided the intent is not changed. The readability of the statement can be tested by sponsors in assessing the performance of their labels.
XXXXXXXXX suggest deleting the word *"with"*, as it could be misinterpreted as referring only to the timing of the doses (implying only that the products should just not be taken at the same time of day). Also noted that two paracetamol-containing products could be taken without exceeding the recommended maximum daily dose. Suggested amendment to: *"Do not take other paracetamol containing products [without seeking medical advice / unless advised by your doctor or pharmacist]"*.	Inclusion of the word *"with"* does not seem to refer only to the timing of the doses. The intent of the words *"unless advised to by a doctor or pharmacist"* is to cover situations where a doctor/pharmacist recommends taking two different paracetamol-containing products at the same time, within the maximum dose range. In some circumstances it may be appropriate to take two paracetamol-containing products at different times of the day (e.g. plain paracetamol during the day and paracetamol + sedative (e.g. XXXXXXXXXX) at night.
Alternatively, XXXXXXXXX suggested that the warning should advise that maximum daily doses of paracetamol should not be exceeded, with more specific guidance on large amounts – eg. for adults, not more than 8 tablets per day	The maximum daily dosage is already included in the AGRD2 guideline on paracetamol – this requires advice that dosage should not exceed 4 g (expressed as a number of doses/ tablets etc) in 24 hours.

Other issues:

Responses received	**Comments**
Various respondents were confused as to whether retention of App F warning statements 34 and/or 35 was intended, with the new statements	The proposed statements are intended to replace the current Appendix F warnings.
Retention of the last sentence of App F warning #35 suggested – *"Prolonged or excessive use without medical supervision could be harmful"* [XXXXXXXXX]	While not as explicit, the first statement (*Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor*) is intended to re-state this warning in a more positive way.
Revision of App F warning #35 suggested – *"CAUTION – This preparation is for the relief of minor and temporary ailments"* [XXXXXXXXX]	Unnecessary, as the specified indications in AGRD2 refer to temporary relief and are restricted to minor conditions.
Concerns that proposed statements should be considered in light of current consumer focussed, performance-based labelling initiatives being undertaken by XXXXXXXXX, and states that new performance-based XXXXXXXXXX labels address the main points (except for reference to liver damage and inclusion of the PIC phone no). [XXXXXXXXX]	The proposed statements are intended to simplify and rationalise the existing warning statements while adding extra statements in relation to overdose with paracetamol and the need to avoid doubling-up. Under proposals being developed for consumer-focused labelling, sponsors will be able to modify the statements (provided the intent is the same) to maximise their performance for consumers.
Concerns re equity across relevant non-prescription analgesics and other OTC medicines [XXXXXXXXX]	The additional statement for paracetamol was recommended by the MEC because the effects of paracetamol overdose are more serious, resulting in delayed, potentially fatal liver damage. Overdose with the other analgesics does not have these effects.
Request that any statements should be market tested prior to being implemented, to ensure their full intent will be met [XXXXXXXXX]	Sponsors are at liberty to market test their labels as part of product development. Detailed guidelines for doing this are being developed as part of the consumer-focused labelling project.

NSAIDS

Warning statements recommended by the MEC (April 2003)

Aspirin, Ibuprofen, Naproxen and Mefenamic acid

Don't use [this product / name of the product]:
- **If you have a stomach ulcer;**
- **In the last 3 months of pregnancy** *[for naproxen and mefenamic acid – may be omitted in preparations for the treatment of dysmenorrhoea***];**
- **If you are allergic to [aspirin/ ibuprofen/ naproxen/ mefenamic acid] or anti-inflammatory medicines.**

Unless a doctor has told you to, don't use [this product / name of the product]:
- **For more than a few days at a time;**
- **If you have asthma;**
- **In children under 12 years of age** *[for aspirin only]***; or**
- ***If you are pregnant*** [for naproxen and mefenamic acid – may be omitted in preparations for the treatment of dysmenorrhoea]

For aspirin only:

See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. [Can be omitted in products for inhibition of platelet aggregation or with additional active ingredients]

For use under medical supervision only [For products for inhibition of platelet aggregation and sustained release preparations containing 650 mg or more of aspirin]

Consult a doctor before giving the medication to children or teenagers with chicken pox, influenza or fever
[Current statement (App F no 37) to be retained pending further evaluation by the MEC]

Comments:

Responses received	Comments
XXXXXXXXX suggested amendment of *"Don't use [this product / name of the product]: …If you are allergic to aspirin* [etc] *or anti-inflammatory medicines"* to *"…If you are allergic to aspirin or taking other medicines containing aspirin* [etc]*"* as consumers would not understand the term, *"anti-inflammatory medicines"*.	This statement was intended to cover people who are allergic to any NSAID (not just the one being taken). It is agreed that the term 'anti-inflammatory medicine' may not be familiar to some consumers but the alternatives (e.g. NSAIDs) are similar. Any suggestions for an alternative to the term *"anti-inflammatory medicines"* welcome? An extra dot point could be added following *"Unless a doctor has told you to, don't use [name]:* • *With other products containing [aspirin etc]* This would also address calls for a more even handed approach with paracetamol (see above).
A warning about not taking ibuprofen with other products containing ibuprofen should be added. In addition, more than one NSAID should not be taken concurrently. [XXXXXXXXX]	See above
Statements similar to those proposed for paracetamol re overdose, contacting the PIC, not exceeding recommended doses, not taking the product for more than a few days, should be required (and for all medicines in general) [XXXXXXXXX]	The warning statement for paracetamol is specific for that drug. It does not apply to the other analgesics (see above).
Statements about not taking aspirin, ibuprofen and naproxen with anticoagulants should also be considered [XXXXXXXXX]	Warnings about drug interactions with OTC medicines are covered in the AGRD2 or required at the time of evaluation (currently specified for aspirin and ibuprofen in AGRD2). Appendix F of the SUSDP does not cover warnings about drug interactions (except with alcohol).

Responses received	**Comments**
Duplication between requirements of SUSDP, AGRD2 and TGAC (particularly for ibuprofen) needs to be addressed [XXXXXXXXX]	There is a proposal to amend the *Therapeutic Goods Advertising Code* to remove the reference to labelling for analgesic warning statements in the Code. Duplication relating to use during pregnancy in the AGRD2 can be addressed once the SUSDP statements finalised.
Proposed statements do not include current AGRD2 interaction precautions [XXXXXXXXX]	The interaction statements will still be required by AGRD2 (for aspirin and ibuprofen) and applied at the time of registration (naproxen). In addition, see comment above
XXXXXXXXX opposes statement relating to asthma for naproxen and mefenamic acid – unless there is evidence to demonstrate that asthma can be aggravated by naproxen / mefenamic acid	The MEC has required this statement in registering all NSAIDs on the basis that this is a class reaction applicable to all NSAIDs. PIs for naproxen (eg. XXXXXXXXXX) and mefenamic acid (eg. XXXXXXXXXX) include as a Contraindication, patients in whom aspirin or other NSAIDs induce allergic symptoms including asthma/bronchospasm (consistent with ibuprofen PIs, eg. XXXXXXXXXX, XXXXXXXXXX). Martindale refers to a study showing reactions (rhinorrhoea, chest tightness, wheezing, dyspnoea) in aspirin-sensitive patients who were given naproxen 40-80 mg. It also states that hypersensitivity to individual NSAIDs is believed to be closely linked to the extent they inhibit prostaglandin. The efficacy of naproxen and mefenamic acid in dysmenorrhoea is related to inhibition of prostaglandins.
PIC phone number should be included on all medicine labels (including NSAIDs), not just paracetamol [XXXXXXXXX]	This is a broader issue that would need to be referred to the Therapeutic Goods Committee for consideration for inclusion in the Labelling Order. It would not be appropriate to include this as a general requirement via the SUSDP.

Responses received	Comments
For mefenamic acid – Unless the S2 entry is to be changed, references to pregnancy could be deleted, as mefenamic acid is currently only OTC in preparations for dysmenorrhoea	Agreed

No specific comments were received on the other proposed statements.

General comments

Responses received	Comments
Questions as to whether current SUSDP Appendix F statements would still apply	The new requirements would replace current statements.
Further consideration/market testing of proposed warning statements before implementation to ensure they convey the intended meaning to consumers [XXXXXXXXX, XXXXXXXXX];	Under proposals being developed for consumer-focused labelling, sponsors will be able to modify the statements (provided the intent is the same) to maximise their performance for the benefit of consumers.
Advice should be sought from experts in written communication and from consumers before implementation [XXXXXXXXX]	Detailed guidelines for doing this are being developed as part of the consumer-focused labelling project.
The SUSDP should allow flexibility of wording [XXXXXXXXX].	The SUSDP does allow flexibility of wording (provided the intent is not changed) – this would cover appropriate combinations.
NDPSC should ensure flexibility is allowed in the wording and positioning of all required warning statements [XXXXXXXXX]	Agreed
The SUSDP should emphasise the acceptability of appropriate combinations of SUSDP App F statements [XXXXXXXXX]	Agreed
All warning statements should be enforceable for new and existing products [XXXXXXXXX]	The SUSDP applies to <u>all</u> scheduled products (current and new).

ATTACHMENT 4 – REVISED WARNING STATEMENTS – ITEM 17.1

PARACETAMOL

Adults:
Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.

Children and adolescents:
Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131 126; New Zealand 0800 764 766) or go to a hospital straight away, even if you feel well, because of the risk of delayed, serious liver damage.

Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.

ASPIRIN

Don't use [this product / name of the product]:
- *If you have a stomach ulcer;*
- *In the last 3 months of pregnancy;*
- *If you are allergic to aspirin or anti-inflammatory medicines.*

Unless a doctor has told you to, don't use [this product / name of the product]:
- *For more than a few days at a time;*
- *With other medicines containing aspirin or other anti-inflammatory medicines;*
- *If you have asthma;*
- *In children under 12 years of age;*
- *If you are pregnant.*

See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. [Can be omitted in products for inhibition of platelet aggregation or with additional active ingredients]

For use under medical supervision only [For products for inhibition of platelet aggregation and sustained release preparations containing 650 mg or more of aspirin]

Consult a doctor before giving the medication to children or teenagers with chicken pox, influenza or fever [Current statement (App F no 37) to be retained pending further evaluation by the MEC]

IBUPROFEN

Don't use [this product / name of the product]:
- *If you have a stomach ulcer;*
- *In the last 3 months of pregnancy;*
- *If you are allergic to ibuprofen or anti-inflammatory medicines.*

Unless a doctor has told you to, don't use [this product / name of the product]:
- *For more than a few days at a time;*
- *With other medicines containing ibuprofen or other anti-inflammatory medicines;*
- *If you have asthma;*
- *If you are pregnant.*

NAPROXEN

Don't use [this product / name of the product]:
- *If you have a stomach ulcer;*
- *In the last 3 months of pregnancy* [may be omitted in preparations for the treatment of dysmenorrhoea]*;*
- *If you are allergic to naproxen or anti-inflammatory medicines.*

Unless a doctor has told you to, don't use [this product / name of the product]:
- *For more than a few days at a time;*
- *With other medicines containing naproxen or other anti-inflammatory medicines*
- *If you have asthma;*
- *If you are pregnant.* [may be omitted in preparations for the treatment of dysmenorrhoea]

MEFENAMIC ACID

Don't use [this product / name of the product]:
- *If you have a stomach ulcer;*
- *If you are allergic to mefenamic acid or anti-inflammatory medicines.*

Unless a doctor has told you to, don't use [this product / name of the product]:
- *For more than a few days at a time;*
- *With other medicines containing mefenamic acid or other anti-inflammatory medicines;*
- *If you have asthma.*