Australian Government

Department of Health and Ageing

National Drugs and Poisons Schedule Committee

Record of Reasons

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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

1.8.1.2.1 UNSCHEDULED INJECTABLES

PURPOSE

The Committee considered harmonisation of the regulation of injectable preparations.

BACKGROUND

A class entry for injectable medicines was listed under Part III (equivalent to Schedule 2) in the New Zealand (NZ) medicines classification category while the control of injectables in Australia was associated with the scheduling of the substance, where specified.

The June 2003 NDPSC meeting considered the following policy questions raised by the TTHWP(M) June 2003 meeting (revised Recommendation 8/7):

- 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 AUSTRALIA;
- 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 June 2003 meeting was advised that there was no evidence of any problem associated with the use of injectable preparations in developed countries including Australia and NZ, based on extensive literature review. On this basis, the Committee agreed that there was no need to control such preparations through scheduling at this time and that should new evidence to the contrary come to light in the future, the matter would be considered on a case-by-case basis.

DISCUSSION

A Member recalled that the initial recommendation to the TTHWP on medicines to regulate the use of injectable medicines was based on concerns relating to abuse of injectable vitamins and minerals, homoeopathic, salt and sugar preparations. A literature review was subsequently undertaken to investigate the issue over a two-year period but no evidence of abuse or misuse in either country was uncovered and a harmonised position with Australia was supported.

Members were advised that removal of the class entry for injectable medicines from Part III was not likely to have a negative impact on public health outcomes in NZ as controls

on injectable medicines would still be covered by the scheduling of the active ingredient(s), as was the case in Australia.

The Committee was informed that the Adverse Drug Reaction Unit was monitoring the issue relating to medication errors reported in Australia associated with intravenous preparations containing potassium chloride in wards and other patient-care areas. Members were advised that XXXXXXXXXXXX was finalising an Alert on IV Potassium solutions which included recommendations and an action plan to address the problems identified.

Members were advised that a "warning alert" would soon be issued concerning the dangers of potassium chloride injections with recommendations regarding storage etc. and that the TGA was pursuing a proposal to colour code labels on medicines to highlight the danger.

The Committee agreed that scheduling was not an appropriate mechanism for addressing issues relating to use of medicines in hospitals and that there was no need for a generic entry in the SUSDP for injectable preparations at this time.

OUTCOME

The Committee agreed to recommend to NZ Ministry of Health to harmonise with Australia by deleting the Part III class entry for injectable medicines. This recommendation was made on the grounds of harmonisation and the absence of evidence associated with abuse or misuse of injectable preparations in either country.

1.8.1.2.2 FLUORIDES

PURPOSE

The Committee considered TTHWP Recommendation 9/1 to delete the term "dentifrice" from the fluoride entries in the SUSDP to harmonise with New Zealand (NZ).

BACKGROUND

The TTHWP 9th Meeting (June 2003) agreed to recommend to the NDPSC (Recommendation 9/1) that the Schedule 2,3 and 4 entries for fluorides be amended to remove the term "dentifrice" and harmonise with NZ. The cut-offs for fluorides in Schedule 4 and 2 were already harmonised.

The Schedule entries for fluorides for therapeutic use in the SUSDP contained the term "dentifrice" but no definition was ever included in SUSDP Part 1. In the absence of a definition for dentifrice in the SUSDP, the common dictionary definition is implied such as "abrasive substance for use in cleaning the teeth" and "toothpaste or tooth powder from the root *frico* to rub". The fluoride entries in the NZ medicine classification categories referred specifically to pastes, powders or gels for the cleaning of teeth. The TTHWP

June 2003 meeting noted that the existing definitions for dentifrice in Australia and NZ were difficult to harmonise as the dictionary definition could not be modified and any change to the fluoride entries NZ classification categories to include a definition for "dentifrice" would require an amendment to the Medicines Act. On this basis, the TTHWP recommended that the simplest approach to harmonise with NZ was to amend the fluoride entries in the SUSDP to specify "pastes, powders or gels for the cleaning of teeth".

DISCUSSION

A Member advised that the term "dentifrice" as used in NZ incorporates a whole range of oral hygiene products including toothpastes and mouthwashes, and is only used as part of the definition for "related products" in NZ legislation. If the Australian definition was adopted, a whole range of dental hygiene products already on the market in NZ would be adversely affected irrespective if such products were appropriately labelled. Furthermore, the Member also sought advice with regard to the regulatory status of mouthwashes in Australia following implementation of the new devices legislation. If fluoride mouthwashes were covered by the new devices legislation, Pharmacy Only (Schedule 2) products in NZ may be available as unrestricted products in Australia irrespective of the harmonised scheduling entries.

It was agreed to seek further information from the Office of Devices, Blood and Tissues (ODBT) to clarify the regulatory status of fluoride-containing mouthwashes in Australia.

OUTCOME

The Committee agreed to replace the term "dentifrice" in the SUSDP with "pastes, powders or gels for the cleaning of teeth" to harmonise with NZ and foreshadow consideration of this decision at the February 2004 meeting.

Foreshadowed for consideration at the February 2004 meeting

Schedule 2 - Amendment

FLUORIDES - amend entry to read:

FLUORIDES for human therapeutic use (**except** in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):

(a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or

(b) in preparations for topical use containing 2.5 per cent or less of fluoride ion **except**:

(i) pastes, powders or gels for the cleaning of teeth included in Schedule 3;

(ii) pastes, powders or gels for the cleaning of teeth containing 1000 mg/kg or less of fluoride ion; or

(iii) other dental hygiene products containing 100 mg/kg or 100 mg/L or less of fluoride ion.

Schedule 3 - Amendment

FLUORIDES - amend entry to read:

FLUORIDES in pastes, powders or gels for the cleaning of teeth containing more than 1000 mg/kg of fluoride ion.

Schedule 4 - Amendment

FLUORIDES - amend entry to read:

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

(a) when included in Schedule 2 or 3;

(b) pastes, powders or gels for the cleaning of teeth containing 1000 mg/kg or less of fluoride ion;

(c) other dental hygiene products containing 100 mg/kg or 100 mg/L or less of fluoride ion; or

(d) in other substances containing 15 mg/kg or 15 mg/L or less of fluoride ion.

Schedule 5

FLUORIDES - amend entry to read:

FLUORIDES in preparations containing 3 per cent or less of fluoride ion **except**:

(a) when included in Schedule 2, 3 or 4;

(b) in pastes, powders or gels for the cleaning of teeth containing 1000 mg/kg or less of fluoride ion; or

(c) in preparations containing 15 mg/kg or less of fluoride ion.

Schedule 6

FLUORIDES - amend entry to read:

FLUORIDES **except**:

(a) when included in Schedule 2, 3, 4 or 5; or

(b) when separately specified in this Schedule; or

(c) in pastes, powders or gels for the cleaning of teeth containing 1000 mg/kg or less of fluoride ion; or

(d) in preparations containing 15 mg/kg or less of fluoride ion.

1.8.1.2.3 SEDATING/HYPNOTIC ANTIHISTAMINES (PROMETHAZINE, DOXYLAMINE AND DIPHENHYDRAMINE)

PURPOSE

The Committee considered Decision 9/3 of the June 2003 TTHWP meeting to harmonise the scheduling of hypnotic antihistamines, specifically promethazine, doxylamine and diphenhydramine.

BACKGROUND

The October 2002 TTHWP meeting noted that promethazine, diphenhydramine and doxylamine for the treatment of insomnia or anxiety was included in Part II (S3) in New Zealand for 10 doses or less, with all other oral uses included in Part III (S2) or General Sale. Above ten doses, such products were included in Part I (S4). In Australia, the same use (treatment of insomnia or anxiety) was covered by the Schedule 3 entry, which specifies oral preparations irrespective of pack size.

The June 2003 TTHWP meeting considered the NZ MOH literature review on antihistamines which recommended that sedating antihistamines should be more restrictively classified compared to non-sedating antihistamines. Based on the findings of the review, the TTHWP agreed to recommend harmonisation with the Australian approach of scheduling sedating or hypnotic antihistamines as S3 and non-sedating antihistamines as Schedule 2. Further details of the TTHWP decision (8/8) are outlined under Item 18.4 – Sedating Antihistamines.

DISCUSSION

The Committee noted that there were no products in Australia containing diphenhydramine or doxylamine for the prevention or treatment of travel sickness, and that such substances were mainly used in cough and cold preparations and products for

aid in sleeping. However, the diphenhydramine entry in Schedule 2 still included motion sickness products, which should be deleted to harmonise with NZ, and for consistency with the S2 entry for doxylamine.

Accordingly, the Committee agreed that the harmonisation issues surrounding the use diphenhydramine and doxylamine for treatment of insomnia or anxiety was best addressed with other sedating antihistamines under Item 18.4.

With regard to promethazine, it was highlighted that there was only a need to address the harmonisation of scheduling for the treatment or prevention of travel sickness. Further details concerning the discussion of promethazine for travel sickness can be found under Item 1.8.1.2.3.1.

1.8.1.2.3.1. PROMETHAZINE

PURPOSE

The Committee considered TTHWP Decision 9/4 where it was recommended that harmonisation of the scheduling of meclozine, promethazine and dimenhydrinate for the prevention of travel sickness could not be harmonised due to legislative differences.

BACKGROUND

The October 2002 TTHWP meeting noted that in New Zealand the specific use of promethazine in a sealed container of not more than 12 tablets or capsules for the prevention of travel sickness were general sales when sold at a transport terminal or aboard a ship or plane. In Australia packs of 10 doses or less for the same use are included in Schedule 2.

The June 2003 TTHWP noted that in Australia the mechanism to allow sale of small packs of travel sickness tablets from outlets other than pharmacies varied from jurisdiction to jurisdiction. While the current scheduling was the same between the two countries, there was no equivalent or common mechanism that could be included in the SUSDP to allow harmonisation of supply with NZ. Accordingly, there was no support from TTHWP members for further deregulating this use of promethazine and agreed that NDPSC should be advised that the entries are unable to be harmonised due to the differing legislative environments in the Australian jurisdictions and NZ. It was recommend that the relevant entry for promethazine be added to the list of entries for review after two years.

DISCUSSION

The Committee noted while that the NZ entry for promethazine in Part III (S2) provided an exemption for small packs of promethazine theoclate for the prevention of travel sickness, such medicines in NZ were labelled as Schedule 2 products. It was outlined that the additional provision to allow the sale in authorised travel outlets in NZ were

similar to that already in place in Australian jurisdictions where poisons licence holders were allowed to sell certain poisons where there is no pharmacy within a certain distance. On this basis, members were of the view that harmonisation of regulatory outcome in terms of control on supply had been achieved.

Majority of State and Territory Members expressed a view that harmonisation of control on supply was best achieved through individual State and Territory Poisons legislation. This approach ensured a harmonised outcome across the jurisdictions including NZ, and maintained the current arrangement in Australian jurisdictions where outlets wishing to obtain a poisons licence for retail purposes were assessed for fitness to supply.

It was considered that the availability of travel sickness tablets at the departure side of Australian international airport terminals but not domestically appeared to be inconsistent.

OUTCOME

Accordingly, the Committee agreed to foreshadow the decision to harmonise the scheduling outcome with NZ and include preparations for the prevention or treatment of motion sickness in S2 with exemption for preparations containing promethazine theoclate in a sealed container containing 12 or less such tablets or capsules for the prevention of travel sickness.

The Schedule 2 entry below has been adjusted for consistency with foreshadowed Schedule entries for other sedating histamines discussed under Item 18.4.

Foreshadowed for consideration at February 2004 meeting

Schedule 2 - Amendment

PROMETHAZINE – amend entry to read:

PROMETHAZINE:

(a) in preparations for the prevention or treatment of motion sickness not labelled for the treatment of children under two years of age **except** in primary packs containing 12 or less such tablets or capsules; or

(b) in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing promethazine in a night time dose; and

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

1.8.1.2.3.2 MECLOZINE

PURPOSE

The Committee considered TTHWP Decision 9/4 where it was recommended that harmonisation of the scheduling of meclozine, promethazine and dimenhydrinate for the prevention of travel sickness could not be harmonised due to legislative differences.

BACKGROUND

The October 2002 meeting of the TTHWP noted that meclozine for the prevention of travel sickness was included in Part III (S2) in NZ, and that small packs were allowed to be sold as general sales medicines in specified outlets such as transport terminals or aboard a ship or plane. In contrast, all products containing meclozine were in Schedule 4 in Australia, due to concerns regarding possible teratogenic effects.

DISCUSSION

A Member proposed an exemption from scheduling of small packs of meclozine for use in travel sickness, for consistency with the approach taken for promethazine (see item 1.8.1.2.3.1).

The Committee was advised that there were no existing products listed on the ARTG for supply in Australia. However, Members supported deferring further consideration of this matter to the February 2004 meeting, to allow advice to be sought from the ADEC on the issue of teratogenicity.

OUTCOME

Accordingly, the Committee agreed to reconsider this matter at the February 2004 meeting.

1.8.1.2.3.3 DIMENHYDRINATE

PURPOSE

The Committee considered TTHWP Decision 9/4 where it was recommended that harmonisation of the scheduling of dimenhydrinate, meclozine and promethazine for the prevention of travel sickness could not be harmonised due to legislative differences.

BACKGROUND

The October 2002 meeting of the TTHWP noted that dimenhydrinate for the prevention of travel sickness was included in Part III (S2) in NZ, and that small packs were allowed to be sold as general sales medicines in specified outlets such as transport terminals or aboard a ship or plane. In Australia packs of 10 doses or less for the same use are included in Schedule 2.

OUTCOME

The Committee agreed to foreshadow a decision to exempt from scheduling small packs of dimenhydrinate for use in travel sickness, for consistency with the approach taken for promethazine (see item 1.8.1.2.3.1).

Foreshadowed for consideration at February 2004 meeting

Schedule 2 - Amendment

DIMENHYDRINATE – amend entry to read:

DIMENHYDRINATE:

(b) in preparations for the prevention or treatment of motion sickness not labelled for the treatment of children under two years of age **except** in primary packs containing 12 or less such tablets or capsules; or

(b) in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing dimenhydrinate in a night time dose; and

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

1.8.1.2.4 NITROFURAN

PURPOSE

The Committee considered the recommendation of the 9th TTHWP (June 2003) meeting in relation to removal of nitrofuran, nifursol and nimorazole from Schedule 4 (S4) of the SUSDP to harmonise with New Zealand.

BACKGROUND

Nitrofuran was initially used as a growth promotant in animal feedstuffs. In 1992, the Committee agreed to include nitrofuran in S4 of the SUSDP based on the toxicology information available, and discontinued its therapeutic use in food-product animals and as animal feeds. Nifursol is a veterinary antiprotozoal, nimorazole is a human therapeutic antiprotozoal, and both are currently included in S4.

The 9th TTHWP (Medicines) June 2003 meeting considered the harmonisation of nitrofuran, nifursol and nimorazole and recommended that the NDPSC remove these chemicals from S4 entry of the SUSDP, given that there were no registered products in Australia and New Zealand.

DISCUSSION

Members noted that new antiprotozoal products would require assessment by the TGA or APVMA prior to registration, and that deleting the S4 entries for nitrofuran, nifursol and nimorazole in the SUSDP would have no regulatory impact, given the absence of registered products in either Australia or NZ. The Committee also emphasised that non-inclusion of chemicals in the SUSDP did not equate to their suitability for exemption from scheduling, and equally, did not mean automatic inclusion in Appendix B.

DECISION – 2003 / 39 – 1

The Committee agreed to delete the Schedule 4 entries for nitrofuran, nitrofursol and nimorazol to harmonise with NZ. No regulatory impact was expected as a result of these amendments.

SCHEDULE 4 – AMENDMENTS

NITROFURAN – delete entry

NITROFURSOL - delete entry

NIMORAZOL - delete entry

1.8.1.2.5 NIFURSOL

See 1.8.1.2.4 Nitrofuran

1.8.1.2.6 NIMORAZOLE

See 1.8.1.2.4 Nitrofuran

1.8.1.3 MATTERS ARISING FROM NDPSC CONSIDERATION OF TTHWP ITEMS

1.8.1.3.1 HYDROQUINONE

PURPOSE

The Committee considered TTHWP Recommendations 8/2 and 9/2 that NZ consider adopting an equivalent entry to Australia in Part 1 (S4) and Part III (S2) respectively for hydroquinone (HQ) and 9/2 entry for hydroquinone (HQ).

BACKGROUND

HQ and its derivatives are commonly used as cosmetic and therapeutic skin and hair-bleaching agents. Hypersensitivity or hyper-pigmentation may occur following use of concentrations above 2% or chronic application to skin. The primary entry for HQ was in S4 of the SUSDP, while preparations for human external therapeutic or cosmetic use containing 2% or less HQ were in S2, and hair preparations containing 1% less HQ were exempt. The main entry for HQ in NZ was in Part III (S2) while medicines containing 2% or less were 'general sale'.

The 8th (October 2002) TTHWP(M) recommended that NZ adopt a Part I entry for HQ to harmonise with Australia (Recommendation 8/2), due to potential risk of hypersensitivity or hyper-pigmentation following use of preparations containing >2% HQ or chronic application to skin. This recommendation was confirmed at the 9th Meeting TTHWP(M) in June 2003 (Recommendation 9/2). Of main concern to the WP was the potential for HQ to mask melanomas given the prevalence of skin cancers in Australia and New Zealand. There was one product for general sale in NZ containing 2% HQ. Accordingly, TTHWP recommended on public health grounds, that NZ MOH harmonise with the more restrictive Australian scheduling and adopt an entry in Part III entry for products containing 2% or less of hydroquinone and an entry in Part I for medicines containing above 2% HQ.

DISCUSSION

Members were informed that in NZ the Environmental Risk Management Authority (ERMA) regulated cosmetics including hair-care products and that harmonisation of their scheduling could not be achieved at this time. The NZ Member confirmed that this decision would have minimal impact in NZ in that there was only 1 registered product containing 2% of HQ, which would be rescheduled from general sale to Part III (S2).

OUTCOME

The Committee endorsed Decision 8/2 and 9/2 of the TTHWP (M) and recommended that NZ MOH consider on public health grounds:

- adopting an equivalent Part I entry for hydroquinone; and
- adopt a similar regulatory outcome for the hydroquinone in Part III for products containing 2% or less of hydroquinone

1.8.1.3.2 PARACETAMOL

PURPOSE

The Committee considered the proposed Schedule 4 (S4) entry for paracetamol foreshadowed at the June 2003 meeting.

BACKGROUND

The June 2003 NDPSC meeting agreed to adopt TTHWP Decision 8/5 and foreshadowed an amendment to the S4 entry for paracetamol for consideration at the October 2003 meeting and an amendment to the Schedule 2 (S2) entry for consideration at the October 2004 NDPSC meeting. This staged approach was based on the premise that whilst harmonisation of prescription medicines may be appropriate at this time, scheduling harmonisation of OTC paracetamol could not be achieved until the Warning Statements (WS) in the 'reverse scheduling' provisions were incorporated into the new Medicines Labelling Order (MLO), which was expected to be given effect on 1 July 2004. Accordingly, the NDPSC endorsed Decision 8/5 to NZ Ministry of Health (MOH) for consideration.

The S2 amendment foreshadowed for consideration at the October 2004 meeting relating to paracetamol removed the "reverse scheduling" provisions, ie. inclusion of specified WS on the label as a condition for exemption from the requirements of scheduling, in anticipation of the transfer of such WS to the new MLO.

NZ had previously agreed to adopt the Australian pack size limit of 12.5 g of paracetamol for exempt tablet and capsules, once the labelling guidelines for paracetamol were harmonised.

DISCUSSION

The Committee was informed that the S2 entry foreshadowed at the June 2003 meeting exceeded the agreed harmonised pack size with NZ of 12.5 g paracetamol for exempt preparations. In addition, it was highlighted that the foreshadowed S4 entry, if adopted, would reschedule to S4 a sustained-release product containing 665 mg paracetamol while the foreshadowed S2 entry, if amended to 665 mg, would exempt the same product from scheduling.

Members noted that the statement "not labelled for the treatment of children under 7 years of age" had been changed to "not labelled for the treatment of children 6 years of age or less" in the foreshadowed S2 entry. The Committee agreed to the amendment for

consistency with the wording used in S2 for antihistamines although the intent remained unchanged.

OUTCOME

The Committee agreed that the S2 entry foreshadowed for October 2004 should be amended to reflect the following principles:

- Liquid oral preparations remained appropriate in S2;
- Suppositories remained appropriate in S2;
- Preparations compounded with other S2 substances remained appropriate in S2. (See item 18.4 for further details on the consideration of combined preparations containing paracetamol and other active ingredients including antihistamines.)
- Tablets or capsules containing 500 mg or less of paracetamol as the only therapeutically active ingredient in a pack containing 12.5 g or less of paracetamol be exempt from scheduling, provided such packs were not labelled for the treatment of children 6 years of age or less;
- Tablets and capsules containing 665 mg or less of paracetamol with no restriction on pack size remained appropriate in S2;
- Paediatric preparations to remain in S2;
- Individually wrapped powders or sachets of granules containing 1000 mg or less of paracetamol, with no pack size restriction, remained appropriate in S2; and
- Individually wrapped powders or sachets of granules containing 1000 mg or less of paracetamol are exempt from scheduling when in a pack containing 12 g or less of paracetamol, containing no other therapeutically active constituent other than effervescent agents, and not labelled for the treatment of children 6 years or less.

DECISION 2003/39 - 2

The Committee agreed to amend the S4 entry foreshadowed at the June 2003 to restore tablets or capsules containing 665 mg or less but more than 500 mg of paracetamol with no pack size restriction in S2. In addition, the Committee confirmed the following:

- the inclusion in S4 of tablets or capsules containing greater than 665 mg paracetamol and individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol, with no pack size restriction, remained appropriate on the basis of public health and safety; and

- paracetamol when combined with aspirin, caffeine, or salicylamide or any derivative of these substances remained appropriate in S4. (Refer to Item 14.1.2)

Schedule 4 - Amendment

PARACETAMOL – amend entry to read:

PARACETAMOL:

(a) when combined with aspirin, caffeine or salicylamide or any derivative of these substances **except** when separately specified in the Schedules;

(b) in tablets or capsules containing more than 665 mg of paracetamol; or

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

Schedule 2 - Amendment (Foreshadowed for consideration at October 2004 meeting pending transfer of warning statements to the TGA)

PARACETAMOL – amend entry to read:

PARACETAMOL for therapeutic use in:

(a) liquid oral preparations;

(b) suppositories;

(c) 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 where the paracetamol is the only therapeutically active constituent other than effervescent agents, and not labelled for the treatment of children 6 years of age or less; or

(d) tablets or capsules each containing 665 mg or less of paracetamol **except** when containing 500 mg or less of paracetamol per dose in a primary pack of 12.5 g or less of paracetamol as the only therapeutically active constituent, when:

(i) packed in blister or strip packaging or in containers with child-resistant closures; and

(ii) not labelled for the treatment of children 6 years of age or less,

except when included in Schedule 3 or 4.

1.8.1.3.3 ASPIRIN

PURPOSE

The Committee considered the foreshadowed Schedule 2 (S2) amendment for aspirin to harmonise with NZ the scheduling of low-dose preparations for the prevention of cardiovascular disease and inhibition of platelet aggregation.

BACKGROUND

The primary entry for aspirin was in Schedule 2 for Australia and Schedule 3 (Part II) for New Zealand (NZ) with exemptions to general sales in both countries. The entries were also not harmonised with regard to dosage limits, pack size restrictions and warning statements requirements. However, the scheduling of aspirin in NZ did not specify restrictions on dosage or pack size for general sale, standard release preparations and was therefore less restrictive in effect compared to Australia.

The June 2003 NDPSC meeting endorsed the view of the October 2002 TTHWP meeting that final harmonisation of the scheduling of aspirin could not be achieved at the time and that a staged approach would be more appropriate. TTHWP recommended partial harmonisation of S2 entries as a first step, to be followed by final harmonisation when the warning statements were transferred to the new Medicines Labelling Order (MLO), which was expected to come into effect on 1 July 2004. On this basis, the NDPSC endorsed TTHWP Decision 8/4 and foreshadowed the amendment to the S2 aspirin entry to exempt low-dose aspirin for prevention of cardiovascular disease or inhibition of platelet aggregation from scheduling requirements to harmonise with NZ. Furthermore, the NDPSC also foreshadowed a new S2 entry for aspirin for consideration at the October 2004 meeting which no longer carried the warning statements for exempt preparations.

DISCUSSION

Members noted that the foreshadowed S2 entry, if adopted, would effectively raise the level of restriction on aspirin products in NZ as it included restrictions on pack size, dosage, and indications for general sale products. In Australia, the same entry would allow as unscheduled medicines, larger pack sizes of tablets or capsules each containing 100 mg or less of aspirin, when labelled for the prevention of cardiovascular disease and inhibition of platelet aggregation.

DECISION 2003/39 - 3

The Committee noted that there was no public health impediment to prevent the exemption from scheduling of tablets and capsules each containing 100 mg or less of aspirin, in packs containing 100 or less such tablets and capsules, and labelled for the prevention of cardiovascular disease or inhibition of platelet aggregation. On this basis,

the Committee agreed to adopt the foreshadowed S2 entry as published in the June 2003 Record of the Reasons to harmonise with NZ. The entry was, however, amended to incorporate the MEC label warning statements agreed to under Item 13.7.2.

In addition, the Committee also agreed to recommend to NZ Ministry of Health (MOH) that it delete its Part II entry for aspirin and consider adopting the new Schedule 2 entry in Part III (S2).

Schedule 2 - Amendment

ASPIRIN - amend entry to read:

ASPIRIN **except**:

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

(b) in individually wrapped powders or sachets of granules each containing 650 milligrams 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) (A) is labelled with the warning statement (permitted until 30 April 2005):

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; or

(B) is labelled with the warning statements (mandatory from 1 May 2005):

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.]; 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.

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 of not more than 25 tablets or capsules, each containing 325 mg or less of aspirin, or in a primary pack of not more than 16 tablets or capsules, each containing 500 mg or less of aspirin;

(iii) (A) the primary pack is labelled with the warning statement (permitted until 30 April 2005):

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; or

(B) is labelled with the warning statements (mandatory from 1 May 2005):

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.]; 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.

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.

1.8.1.3.4 PYRIDOXINE

PURPOSE

The Committee considered the scheduling, warning statements and cut-off for vitamin B6.

BACKGROUND

Pyridoxine was included in Schedule 4 for recommended daily doses above 50mg when labelled with a specified warning statement in 1985. Pyridoxine is not controlled as a medicine in New Zealand.

The NDPSC considered restricting the availability of pyridoxine in 1985 following advice to the Department of Health linking high intakes of pyridoxine with sensory neuropathy. Recognising the data deficiencies in the toxicological profile, the NDPSC referred the issue to XXXXXXXXXXXX. XXXXXXXXXXXX concluded 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.

Following the inclusion of pyridoxine in Schedule 4, industry requested that the upper limit be set in the range 200-250mg/day. After further consultation with industry, the Committee finalised the current Schedule 4 entry to include other compounds exhibiting Vitamin B6 activity.

A safety evaluation of pyridoxine prepared by the OCM in January 2001 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."

The 38th (June 2003) NDPSC meeting considered the outcomes of the three recent international committees who reviewed the safety of pyridoxine: the UK Expert Group on Vitamins and Minerals (May 2003); the EU Scientific Committee on food (November 2000); and the US Standing Committee on the Scientific Evaluation of Dietary Reference Intakes through its Panel on Folates and other B group Vitamins (1999). The NDPSC agreed that there was sufficient evidence to clearly characterise a significant risk of neuropathy from prolonged use of pyridoxine at doses of ≥ 200mg/day in adults. 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 to high dose multi-dose vials.

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. Accordingly, the inclusion of the 200mg upper limit in the pyridoxine Schedule 4 entry was foreshadowed.

DISCUSSION

Members noted the late pre-meeting submission from XXXXXXXXXX that opposed the proposed recommendation on the following grounds:

- the typical high end daily dose of vitamin B6 is 250mg and the ARTG has 17 products with containing 250mg of Vitamin B6 that will be rescheduled as S4 under the current proposal.
- this is largely an administrative recommendation to facilitate harmonisation.
- CMEC using ADRAC data 1980 and 2000 and international safety reviews concluded that no significant safety problems arose.
- XXXXXXXXXX believes the proposal should not proceed without prior review by Office of Complementary Medicine.

A XXXXXXXXXX Member raised concerns that some companies have products that have contain levels of pyridoxine which are slightly above the 200mg upper limit for exemption from Schedule 4 and they will have to reformulate their product.

DECISION 2003/39 - 4

The Committee reconfirmed its view 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. Additionally, noting the request to allow time for industry to reformulate their product, it was agreed to consider further information to vary the effective date at the next meeting if submitted.

Accordingly, the Committee agreed to the following amendment to Schedule 4 and agreed to recommend to NZ MOH that it adopt a similar regulatory outcome.

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 50mg or less of pyridoxine, pyridoxal or pyridoxamine per recommended daily dose.

Schedule 4 - amendment (Foreshadowed for the October 2004 meeting pending transfer of warning statements to the TGA)

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.

1.8.1.3.5 AMPHOTERICIN

PURPOSE

The Committee considered the foreshadowed inclusion in Schedule 3 of topical preparations for the treatment of oral candidiasis.

BACKGROUND

Amphotericin was listed in S4 of the SUSDP and Part II (S3) in New Zealand. Harmonisation of amphotericin was first considered at the first meeting of the TTHWP(M) but was deferred pending finalisation of the JETACAR Report and Commonwealth Government response to the report.

The harmonisation of scheduling of amphotericin was reconsidered at the 8th (October 2002) TTHWP(M) meeting where it was agreed that there were no public health impediments to prevent harmonisation with NZ (Recommendation 8/11). Accordingly, TTHWP recommended the inclusion of topical preparations containing amphotericin for the treatment of oral candidiasis in Schedule 3.

The 38th (June 2003) NDPSC meeting noted that inclusion of amphotericin for the treatment of oral candidiasis in Schedule 3 would be consistent with nystatin and miconazole for the same use and agreed to foreshadow consideration of this matter at the 39th NDPSC meeting to allow appropriate public consultation.

DISCUSSION

Members noted the pre-meeting submission received from XXXXXXXXXX opposing the inclusion of amphotericin for the treatment of oral candidiasis in S3, based on potential adverse effects and potential for development of resistance. XXXXXXXXXX highlighted the following issues:

- Amphotericin IV was the treatment of choice for most serious systemic fungal infections and first line empirical therapy in the treatment of severe sepsis including patients with impaired immunity.
- Amphotericin is an important antifungal agent for parenteral use and a toxic drug.
- Widespread use of antimicrobial products orally or topically could lead to the emergence of microbes resistant to antibiotics and could lead to a reduced effectiveness as a first-line treatment for severe sepsis.

Some Members were of the opinion that resistance to amphotericin could develop with oral candida. However, given the low systemic absorption (estimated to be up to 9%) from topical use, the Committee agreed that it was not likely to become a significant issue.

OUTCOME

Members agreed to defer further consideration of the matter to the February 2004 meeting to allow advice to be sought from the ADEC on the potential for resistance to develop with topical use of amphotericin for the treatment of oral candidiasis.

1.8.1.3.6 PART 2 LABELS AND CONTAINERS

PURPOSE

The Committee considered a foreshadowed amendment to harmonise labelling requirements for Schedule 8 substances and equivalent controlled substances under the NZ Misuse of Drugs Act.

BACKGROUND

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

The June 2003 meeting considered decision 8/12 of the TTHWP(M) and agreed to foreshadow an amendment to Part 2, paragraph 7(1)(a)(iv) of the SUSDP to harmonise the labelling of substances listed in Schedule 8 but were included in the New Zealand's Misuse of Drugs Act 1975 (MODA). The foreshadowed amendment, which allowed the NZ designation, as specified in the MODA to be included on the label of Schedule 8 medicines in Australia was intended to achieve partial harmonisation in light of legislative differences between the two countries. The following entry was foreshadowed:

- **AMEND PART 2 LABELS AND CONTAINERS 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;

DISCUSSION

XXXXXXXXXX, in a pre-meeting submission advised that there is no need to put "NZ" as letters preceding the NZ designation. It was suggested that the SUSDP proposal be amended to harmonise with the NZ requirements so that the appropriate designation should follow the signal heading eg, "CONTROLLED DRUG (B3)". XXXXXXXXXX

believed that the addition of "NZ" would cause confusion as the average Australian consumer would not automatically link "NZ" to mean New Zealand on a medicine pack. Furthermore, XXXXXXXXXX supported full consultation between the relevant Australian and New Zealand regulatory bodies prior to finalising any SUSDP amendments which impacts on NZ requirements and to ensure that the Australian/New Zealand harmonised product is fully acceptable to both countries.

XXXXXXXXXX Member clarified that the minimum signal heading requirement in NZ is the inclusion of the words "CONTROLLED DRUG" on the label of substance listed in NZ's MODA. It was indicated that the addition of "NZ" or "B3" to the signal heading would be acceptable as per NZ legislation if this would assist in clarifying the intent of the signal heading in Australia. The Member stated that it may be appropriate to use the labelling approach as a model for future harmonisation of substances where legislative differences were identified as impediments to harmonisation.

Another Member highlighted that inclusion of "B3" on the signal heading could potentially cause confusion in the community pharmacies where it may be misinterpreted as Schedule 3. In addition retaining "NZ" in the label may send the wrong message that the labelling requirement applies only to New Zealand.

The Committee recognised the need to communicate the intent of the signal heading in advance to pharmacy organisations in order to avoid confusion.

OUTCOME

The Committee agreed to adopt the foreshadowed decision but removed the term "preceded by the letters NZ" from the entry. The Decision would effectively retain the signal heading "CONTROLLED DRUG" as the label of Schedule 8 medicines which would also meet the requirements of the NZ MODA

The Committee further agreed to refer the amendment to NZ MOH for consideration prior to inclusion in the SUSDP.

PART 2, LABELS AND CONTAINERS SUB-PARAGRAPH 7(1)(a)(iv) – Amendment (Foreshadowed)

PART 2, LABELS AND CONTAINERS SUB-PARAGRAPH 7(1)(a)(iv) –amend entry 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 designation as specified in the New Zealand *Misuse of Drugs Act* (1975) 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;

1.8.1.3.7 NICOTINE IN NRT

PURPOSE

The Committee considered the harmonisation of the scheduling of nicotine when used as an aid in smoking cessation.

BACKGROUND

Scheduled smoking cessation products may be available as general sales medicines in New Zealand (NZ) if sold through smoking cessation clinics under the auspices of authorised healthcare practitioners. Nicotine in chewing gum and transdermal patches were unscheduled (general sales) medicines in NZ and in contrast, all NRT products were scheduled in Australia. In the Australian context, there were no definitions or competencies listed for smoking cessation clinics.

Harmonisation of the scheduling of nicotine in Nicotine Replacement Therapy (NRT) products was initially considered at the November 2000 meeting on the recommendation of the TTHWP (Recommendations 84/6 and 85/6). In a pre-meeting submission, the XXXXXXXXXX advised the Committee to maintain existing controls on Nicotine Replacement Therapy (NRT) products pending the completion of research and other actions to be conducted as part of the National Tobacco Strategy. XXXXXXXXXX was of the view that there was no compelling public health case or evidence to support an immediate change to existing scheduling of NRT to harmonise with NZ. The results of this research were expected by XXXXXXXXXX to provide a more comprehensive evidence base to support development of a policy framework for smoking cessation in Australia. The November 2000 Meeting agreed with XXXXXXXXXX advice and TTHWP Recommendations 84/6 and 85/6 to harmonise with NZ were not adopted at the time. Nicotine in NRT was subsequently included in the list of substances of which harmonisation was to be reviewed in 2 years.

The 37th (February 2003) NDPSC meeting considered the XXXXXXXXXX report prepared on behalf of the XXXXXXXXXX of XXXXXXXXXX, which investigated the barriers that smokers face in accessing smoking cessation programs and products. The Committee agreed to seek further from XXXXXXXXXX on XXXXXXXXXX response

to the recommendations of the XXXXXXXXXX Report from which the Committee could determine an appropriate course of action, which would be consistent with the accepted national policy approach. At this meeting, it was also noted that the 2-year timeframe, specified by the National Coordinating Committee on Therapeutic Goods (NCCTG), within which decisions not to harmonise should be reconsidered, had already expired.

The 38th (June 2003) of the NDPSC considered advice from the XXXXXXXXXX of XXXXXXXXXX raising the following points:

- The XXXXXXXXXX report did not provide definitive evidence to make a decision on whether NRT should be rescheduled to allow wider availability and further investigations would be undertaken to ascertain the potential impact of increasing availability.
- Quit services in Australia did not have the necessary infrastructure to support provision of NRT through existing Quit clinics and adopting an approach which was similar to NZ would significantly increase calls to Quitlines.
- XXXXXXXXXX would provide final advice to the October 2003 NDPSC meeting, following an assessment of the full implications of adopting a measure to make NRT more widely available in Australia.

The 38th (June 2003) meeting also considered an application and agreed to reschedule nicotine lozenges to Schedule 2 to which the Committee agreed. This scheduling change was expected to come into effect on 1 January 2004.

DISCUSSION

Pre-meeting submissions were received from the following stakeholders (See Attachment 1 for summary of comments).

- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;
- XXXXXXXXXX;

- XXXXXXXXXX;
- XXXXXXXXXX; and
- XXXXXXXXXX.

The Committee was advised that in response to the WHO Framework Convention on Tobacco Control statement that governments should implement measures to decrease the toll of smoking to health, XXXXXXXXXX initiated a number of projects. Within XXXXXXXXXX, the key project was to evaluate whether unrestricted availability of smoking cessation treatments delivered public health outcomes and XXXXXXXXXX was of the view that allowing open sale of NRT by itself would deliver a public health benefit.

The Committee discussed the following issues:

- Specifying supply in authorised smoking cessation clinics as a condition for exemption from scheduling of NRT in the SUSDP would be inappropriate, as there were no such clinics specified under any State and Territory legislation in Australia. Removing any restrictions on NRT products appropriate for general sale should also provide the jurisdictions with the ability to develop smoking cessation programs which did not limit the supply of such products in pharmacies.
- Government NRT subsidy in NZ did not allow NRT vouchers to be used outside the pharmacy setting although behavioural intervention was mainly provided by a quit service similar to Australia's QUITline. This in effect discouraged supermarkets from selling NRT in NZ due to the lack of profitability.
- Advice was not received from the XXXXXXXXXX, which was a working group under the inter-governmental committee on drugs. A Member stated that public health policies also took into account advice from non-government charity organisations including XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX. In this case, all three organisations supported widening the availability of NRT as a step towards addressing the problem of tobacco addiction in Australia.
- Is there a potential for chronic use of NRT with unrestricted availability? Based on the available information considered by the Committee, there was no evidence to suggest that unrestricted use of NRT had resulted in harm. Whilst it was not disputed that some people may not be successful in quitting smoking without behavioural or lifestyle intervention, it was also recognised there would be individuals who would succeed with the use of NRT alone. This by itself would be a public health benefit.

OUTCOME

The Committee agreed to foreshadow consideration at the February 2004 meeting the proposal to exempt nicotine in lozenges for consistency with nicotine in chewing gum and transdermal patches. Members considered this proposal to be outside the reference

of the pre-meeting gazette notice which sought public comments in relation to the harmonisation of the scheduling of nicotine in smoking cessation products. Nicotine in lozenges is currently in Part II (Schedule 3) in New Zealand except when supplied in smoking cessation clinics.

DECISION 2003/39 - 5

The Committee agreed to exempt nicotine in gums and transdermal patches from the requirements of scheduling to harmonise the scheduling outcome with New Zealand. The Committee was of the view that widening the availability of NRT products should encourage more smokers to quit smoking, and as a first step, this approach should improve public health outcomes.

Schedule 2 - Amendment

NICOTINE - Amend entry to read:

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

(a) in lozenges; or

(b) in preparations for inhalation.

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 4 – Amendment

NICOTINE - Amend entry to read:

NICOTINE for use as an aid in withdrawal from tobacco smoking (including preparations for nasal administration) **except**:

(a) when included in Schedule 2 or 3;

(b) in chewing gum; or

(c) in preparations for transdermal use.

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

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 foreshadowed at the June 2003 NDPSC Meeting.

BACKGROUND

There is no requirement in the SUSDP specifying the conditions for sale or supply of Schedule 8 poisons specified in Part 3.

XXXXXXXXXX has, as part of its provisions for packaging of Schedule 8 drugs (drugs, of addiction), a requirement that containers of Schedule 8 products are to be sealed so that a broken seal is readily distinguishable. XXXXXXXXXX proposed that similar provisions be included in Part 3 of the SUSDP.

The 38th NDPSC Meeting was informed that most companies routinely packaged drugs of addiction with tamper evident sealing for safety reasons.

The Committee previously supported the foreshadowed proposal for the following reasons:

- increased consumer safety;
- reduction of 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.

DISCUSSION

The Committee discussed pre-meeting comment from the XXXXXXXXXX which advised that sub-clause (c) may be problematic by ignoring imprest stocks of Schedule 8 poisons and suggested that this problem be referred to the XXXXXXXXXX.

Members were informed that the NDPSC Secretariat contacted XXXXXXXXXX but did not receive a response.

A pre-meeting submission from XXXXXXXXXX opposed the new entry on the basis that:

- it does not concur with "Guideline for Tamper-Evident Packaging of Medicines, Complementary health care products and Medical Devices (December 2000)", developed by industry associations and the TGA and State/Territory Health Departments; and
- it will introduce logistical problems in the manufacturing cycle for S8 poisons exacerbated by S8 poisons with a short shelf-life.

It was noted that the concerns raised by XXXXXXXXXX were different to that of deliberate tampering for adulteration, rather the concern being the reduction of the potential for diversion to illicit use or abuse.

A Member, as a hospital pharmacist, discussed the option that hospital pharmacists were exempted under paragraph (c) and therefore the issue raised by XXXXXXXXXX regarding imprest stocks did not apply.

State and Territory Members advised that they preferred inclusion of Schedule 8 packaging provisions in Part 2 instead of Part 3 of the SUSDP. Part 2 of the SUSDP is adopted automatically while Part 3 is only a recommendation to States and Territories.

DECISION 2003/39 - 6

The Committee agreed that it was appropriate to include packaging provisions of Schedule 8 poisons in Part 2 of the SUSDP for safety reasons and to ensure Australian harmonisation.

Part 2 –LABELS AND CONTAINERS

CONTAINERS - New entry

Schedule 8 poisons

25A. (1) A person who supplies any Schedule 8 poison 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.

(2) 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 APPENDIX D - PARAGRAPHS 2 AND 6

PURPOSE

The Committee considered a proposal to amend Paragraphs 2 and 6 of Appendix D.

BACKGROUND

Appendix D of the SUSDP imposes additional controls on the possession and supply of Schedule 4 and 8 poisons. Paragraphs 2 and 6 of Appendix D limit the authority to prescribe those substances listed to a specialist physician or dermatologist.

Certain jurisdictions have provisions that allow general practitioners from rural areas to seek authorisation to prescribe certain substances in Appendix D for individual patients with the support of a specialist. The specialist is required to assess the patient to ensure that the Category X drugs listed in Appendix D Paragraphs 2 and 6 that may be prescribed to women of childbearing age are done so appropriately. However, it was thought that the approvals process led to a reluctance to add substances to Appendix D on the grounds that there would be an additional regulatory burden for medical practitioners and administrative load on health authorities. Furthermore, access to specialists was also highlighted as an issue, particularly in rural and remote areas.

To alleviate these problems it was proposed that Appendix D Paragraph 2 and 6 of the SUSDP be amended to allow specialist physicians and dermatologists to authorise medical practitioners in writing to prescribe or order these drugs for the specific patient for a defined period of time once the other requirements of Paragraphs 2 or 6 had been met.

DISCUSSION

A Member, whilst acknowledging the remoteness of many parts of Australia, was of the view that the current wording of Paragraphs 2 and 6 of Appendix D should be maintained on the grounds that the listed substances are of high risk to the foetus and that it remains appropriate that their availability be restricted to prescription by a specialist physician or dermatologist. Furthermore, the member indicated that treating each request for authorisation separately would allow more control over these substances and was unlikely to result in an additional burden on health authorities.

Concern was expressed at the possibility of empowering specialist physicians or dermatologists to authorise general practitioners to prescribe and in doing so diluting the power of health authorities. Additionally, it was suggested that specialists may not be

supportive of an amendment to Appendix D that would authorise general practitioners to prescribe such substances without appropriate training or approval from the health authorities.

The Members noted that there appeared to be significant differences in the approach to substances with teratogenic potential between States and Territories and that ADEC may wish to review this at some stage in the future.

A Member pointed out that in many cases Appendix D was the only jurisdictional mechanism by which the supply of teratogenic substances could be controlled.

OUTCOME

The Committee agreed that the current entry under Appendix D Paragraphs 2 and 6 remained appropriate on the grounds that the existing wording ensures that Category X drugs listed that may be prescribed to women of childbearing age are done so appropriately by suitably qualified and trained doctors.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

4.1 LABELLING OF SCHEDULE 5 CONTAINERS

PURPOSE

The Committee considered the foreshadowed proposal to amend the labelling requirements for containers included in Schedule 5.

BACKGROUND

The June 2003 NDPSC meeting considered a proposal by XXXXXXXXXX to allow the use of permanent adhesive labels on containers of single application hair dyes included in Schedule 5. This change was proposed as an alternative to embossing or indelibly writing the expressions; “POISON”, “NOT TO BE TAKEN” or “NOT TO BE USED AS A FOOD CONTAINER” as required under Part 2, sub-paragraph 23(1)(b)(iii) of the SUSDP. Whilst the original application covered only hair dye products, the available information indicated that a much wider range of products were affected suggesting that all Schedule 5 containers should be included in the proposed amendment.

The Committee recognising the constraints on industry to comply with the labelling requirements specified under Part 2, sub-paragraph 23(1)(b)(iii) of the SUSDP agreed to extend the proposed amendment to include all containers for Schedule 5 poisons. This approach was seen to provide 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. The Committee also supported the inclusion of a definition for a "permanent adhesive label" in the proposed amendment to avoid the potential for confusion.

DISCUSSION

A Member indicated that the original decision to use embossing on Schedule 5 containers was to combat illiteracy, such that the container could be distinguished as a poison bottle by touch. Therefore, concern was expressed over the potential for increased incidence of poisoning through the use of adhesive labels. However, the members were informed that under Part 2, sub-paragraph 23(1)(b)(iii) a label may also be indelibly written on containers and that this alternative to embossing has been in use for some time.

DECISION 2003/39 - 7

The Committee agreed to endorse the foreshadowed amendment to sub-paragraph 23(1)(b)(iii) in Part 2 of the SUSDP.

PART 2 – LABELS AND CONTAINERS

Paragraph 23 – Amendment

Sub-paragraph 23(1)(b)(iii) – amend entry to read:

> (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.

4.2 CARBON TETRACHLORIDE

PURPOSE

The Committee considered the foreshadowed amendment to the carbon tetrachloride entry in Schedule 7 of the SUSDP.

BACKGROUND

During the consolidation of SUSDP No.17, many inconsistencies and editorial errors were discovered. These discrepancies were examined by the June 2003 NDPSC Meeting and it was agreed to foreshadow the subtle change to the carbon tetrachloride entry ie. from CARBON TETRACHLORIDE **except** in chlorinated rubber based paint containing less than 1 per cent of carbon tetrachloride to CARBON TETRACHLORIDE **except** in chlorinated rubber based paint containing 1 per cent or less of carbon tetrachloride.

The foreshadowed entry change was necessary to provide consistency within the SUSDP and to reflect the original intent of the Committee at the time that the entry was created.

DISCUSSION

The Committee agreed to move forward with this proposal.

DECISION 2003/39 – 8

The Committee agreed to amend the Schedule 7 entry for carbon tetrachloride.

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.

4.3 IVERMECTIN

PURPOSE

The Committee considered the proposal to adopt an additional standard for assessing compliance with child resistant packaging in relation to the scheduling of ivermectin.

BACKGROUND

Ivermectin was considered at the February 2003 NDPSC Meeting. XXXXXXXXXX, the sponsor of a new product (XXXXXXXXXX), requested that the 2% limit included in the Schedule 5 ivermectin entry be amended to accommodate its product. The Committee agreed to include ivermectin preparations containing 3.5% or less of ivermectin in Schedule 5, however a restriction that 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. The ivermectin Schedule 5 amendment came into effect on 1 September 2003.

XXXXXXXXXX product, XXXXXXXXXX will be marketed as a sterile solution for subcutaneous injection packaged in high density polyethylene containers fitted with XXXXXXXXXX that can only be breached by a hollow needle.

XXXXXXXXXX provided written correspondence following the February 2003 Meeting stating that they believed that the packaging of their product complied with the definition of a CRC in the SUSDP. The June 2003 Meeting highlighted that it was the responsibility of the manufacture or packer of a poison required to be fitted with a CRC to comply with these provisions.

Child resistant packaging (CRP) and child-resistant closures are defined in the SUSDP as those that conform to Australian Standard AS1928-2001. AS1928-2001 specifies the requirements for reclosable and non-closable packages which are defined as:

- Reclosable package – containers with closures that, once open, can be reclosed to its original form
- Non-closable package – a package in which a unit of use is individually protected until time of release (eg. blister packs, strip, pouch and sachet).

Following the June 2003 Meeting, XXXXXXXXXX was advised by XXXXXXXXXX that they had not taken account of the definitions for CRC and CRP given in the SUSDP and would be unable to meet the criteria necessary for the inclusion of their product in Schedule 5.

XXXXXXXXXX sought removal of the CRC requirement for their product. Whilst it was acknowledged that their container closure did not comply with the definition of a CRC given in Section 2 of Australian Standard AS1928-2001, it was argued that XXXXXXXXXX is fitted with a closure that renders the contents inaccessible to children and that its contents pose no significant increase in hazard to children over the 2% formulation.

DISCUSSION

The Committee was advised that XXXXXXXXXX also submitted correspondence restating its position in regard to the suitability of its products packaging and indicated that its product would by definition be unable to comply with Section 2 of AS1928-2001 and thus fail to meet the standard.

The XXXXXXXXXX supplied Australian Standard AS4710-2001 for consideration by the Committee as an alternative standard for assessing the capacity of a closure or packaging to render the contents inaccessible to children. Australian Standard AS4710-2001 specifies requirements for non-access and non-contact packages which are defined as:

- Non-access package – a package which incorporates a permanent physical barrier, intended to prevent access to its contents by humans under normal conditions of use.
- Non-contact package – as described above for a non-access package, but additionally, where the contents do not leak or leach or make contact with the user.

It was noted that both Australian Standards (AS4710-2001 and AS1928-2001) are assessed using identical test and quality maintenance conditions. However, the acceptance criteria for AS4710-2001 are more stringent than AS1928-2001 in complete panel tests (10 and 15% failure of packaging acceptable, respectively).

The Committee understood that the following public submissions were received:

- XXXXXXXXXX, consultant psychologist, advised that he believes that the definition of a CRC in the SUSDP is limited and restrictive in that it does not include products which are intended for single use. He supports the inclusion of AS4710-2001 in the SUSDP as a suitable standard for assessing the compliance of CRCs on single-use packaging. XXXXXXXXXX also submitted a copy of a report in which the accessibility of a single-use product by children has been assessed using AS4710-2001 for the information of the Committee.
- XXXXXXXXXX, XXXXXXXXXX and the XXXXXXXXXX all advised they had interest in either ivermectin or CRP and requested the right to make post-Meeting comment.

A Member expressed the opinion that any change to the SUSDP to include the AS4710-2001 would not cover ivermectin on the basis that the packaging will not meet the definition in the standard. Specifically, AS4710-2001 requires that the packaging incorporate a permanent physical barrier, intended to prevent access to its contents by humans under normal conditions. The Committee was advised that under normal conditions of use, a large bore needle is used to access the contents of packaging, thus the product would not meet the definition of a non-access package as described in AS4710-2001. Furthermore, a number of Members expressed concern that repeated puncturing of the butyl rubber cap with a large bore needle would result in leakage of the contents of the package occurring, particularly if the container were to be squeezed.

The Committee was reminded that the Company's product, XXXXXXXXXX which contains 3.15% ivermectin, was included in Schedule 5 on the condition that the container in which it was sold was fitted with a CRC or packaged in such a way as to render its contents inaccessible to children.

During the discussion the Committee sought further information from XXXXXXXXXX regarding the use of XXXXXXXXXX. Specifically, a translation of the use instructions, pictorial description of the injection method used to administer the product and expert advice on whether the closure fitted to the product was likely to render its contents inaccessible to children.

XXXXXXXXXX informed the Committee that XXXXXXXXXX would be administered via an XXXXXXXXXX. The XXXXXXXXXX has a volume of 50 mL and would be filled by XXXXXXXXXX of the XXXXXXXXXX container and XXXXXXXXXX XXXXXXXXXX XXXXXXXXXX XXXXXXXXXX. The Company further informed the Committee that anecdotal evidence from the products use in South America suggested that leakage through the XXXXXXXXXX is unlikely to occur even after repeated XXXXXXXXXX XXXXXXXXXX XXXXXXXXXX due to the viscosity of the solution.

The Company also furnished the Committee with the expert opinion XXXXXXXXXX, consultant psychologist, in which he stated the following in regard to the XXXXXXXXXX container:

- "In my opinion there was no way a child could access the contents. The end user product is contained in a plastic bottle. It is sealed with a rubber diaphragm which in turn is locked onto the bottle by a metal strip. The diaphragm is not intended to be removed by anyone. Access to the content is by inserting a hypodermic needle into the diaphragm. The bottle is sold with a plastic removable screw on/off closure. In itself is not child resistant – but in my opinion could not be removed by a child in a 5 minute time period."

The Committee was of the opinion that based on the information presented by the Company there was sufficient evidence to suggest that the XXXXXXXXXX container and its closure would render its contents inaccessible to children. However, a Member expressed a concern that if the reference to CRC was removed from the ivermectin entry in Schedule 5 there would not be a mechanism to control the closures fitted to products that may in the future be marketed containing 3.5% or less of ivermectin.

The Committee agreed to amend the Schedule 5 entry for ivermectin to include a statement that would allow the approval of packaging by the relevant registration authority in the event that child-resistant closure or packaging criteria could not be meet and the authority was satisfied that container and its closure would render its contents inaccessible to children.

OUTCOME

On the issue of the definition for child-resistant closures and packages, the Committee agreed to delete the current definitions for child-resistant closure and child-resistant packaging and replace these with the following definition for child-resistant packaging:

Foreshadowed for consideration at the February 2004 meeting

PART 1 – INTERPRETATION – AMENDMENT

Sub-paragraph 1.(1) – Amend entry for "Child-resistant closure" and "Child-resistant packaging" to read:

Child-Resistant Packaging: means packaging that is designed or constructed to be significantly difficult for a young child to open, or gain access to the contents of, within a reasonable time but not unduly difficult for adults to use properly, but does not mean packaging which all such children cannot open, or obtain the content of, within reasonable time.

Packaging that:

(1) is reclosable and complies with the requirements of at least one of the following standards.

(i) the International Organization for Standardization Standard ISO 8317:1989 entitled *Child-resistant packaging-requirements and testing procedures for reclosable packages*;

(ii) the British Standards Institution Standard BS EN 28317:1993 entitled *Child-resistant packaging-requirements and testing procedures for reclosable packages*;

(iii) the Canadian Standards Association Standard CSA Z76.1-99 entitled *Reclosable child –resistant packages;*

(iv) the United States Code of Federal Regulations, Title 16, Section 1700.15, entitled *Poison prevention packaging standards* and Section 1700.20, entitled *Testing procedure for special packaging*;

(v) the Australian Standard AS1928-2001 entitled *Child-resistant packages*; or

(2) is approved as child-resistant by any order made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*; or

(3) in the case of a can fitted with a press-on lid, a lid of the design known a "double tight" or "triple tight", or

(4) is in the form of a blister and strip packaging , or

(5) is non-access access packaging that complies with the requirements of Australian Standard AS4710-2001 entitled *Packages for chemicals not intended for access or contact with their contents by humans*,

is deemed to be child-resistant packaging for the purpose of the requirements of the SUSDP.

DECISION 2003/39 - 9

The Committee agreed to amend the Schedule 5 entry for ivermectin to allow the approval of packaging by the relevant registration authority.

Schedule 5 - Amendment

IVERMECTIN for use in animals:

(a) in preparations for the prophylaxis of heartworm in cats and dogs;

(b) in intraruminal implants containing 160 mg or less of ivermectin;

(c) in preparations containing 3.5 per cent or less of ivermectin when packed in child-resistant packaging or in packaging approved by the relevant registration authority; or

(d) in other preparations containing 2 per cent or less of ivermectin.

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

5.1 SUSDP, PART 4

5.1.1 CREOSOTE AND RELATED COMPOUNDS AND FRACTIONS

PURPOSE

The Committee considered the scheduling of creosotes and related compounds or fractions.

BACKGROUND

At the June 2003 meeting, the Committee considered an overview of the draft CICAD on coal tar creosote prepared by the Office of Chemical Safety. The Committee was asked to consider:

- 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.
- whether the marketing of coal-tar creosote as a wood preservative should be limited to industrial use and to licensed applicators.
- 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).
- the appropriateness of coal tar preparations being available for the treatment of psoriasis (and for any other cosmetic uses that may exist).
- the appropriateness of creosote being available in oral pharmaceutical preparations.

The Committee asked that advice be sought from the APVMA, MEC and CMEC regarding the potential impact on existing products should creosote and related substances be scheduled.

DISCUSSION

The Committee was informed that a response was only received from the APVMA. Accordingly, the Committee thought it appropriate to defer consideration of this item until advice was received from MEC and CMEC.

OUTCOME

The Committee noted the absence of the advice requested from MEC and CMEC on the potential scheduling issues affecting OTC and complementary medicines and agreed to defer this agenda item to the February 2004 meeting.

5.1.2 METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL

PURPOSE

The Committee considered the scheduling of methylcyclopentadienyl manganese tricarbonyl (MMT).

BACKGROUND

Methylcyclopentadienyl manganese tricarbonyl (MMT) is an anti-valve seat recession (AVSR) additive in automotive lead replacement petrol (LRP). It is either pre-blended at the refinery or added to unleaded petrol by the vehicle owner. AVSR fuel additives are added to automotive fuels as lubricating agents preventing excessive valve seat wear and recession of the valve seat into the automotive cylinder head. Before phaseout in 2000, the most common AVSR additive was tetraethyl lead. MMT is also an octane enhancer

Three companies import a total of approximately 180 tonnes of MMT into Australia which is blended into LRP by at least 2 bulk fuel companies and into aftermarket fuel additives by 2 fuel additive product companies. It is present in LRP at < 72.6 mg/L (< 0.01% w/w) and in aftermarket additive products at < 118 g/L (< 10% w/w).

NICNAS has assessed MMT as a Priority Existing Chemical.

DISCUSSION

The Committee noted the following points raised in the NICNAS PEC Report:

- MMT is acutely toxic by all routes of exposure. It is metabolised predominantly in the liver. Major acute toxic effects include damage to the lungs by all routes, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness.

- The acute oral and dermal toxicity LD50 values for rats have been determined to be 9-179 and 140-795 mg/kg bw, respectively. While acute inhalation studies have indicated LD50 values of 0.22 – 0.25 mg/L (1 hour) and greater than 0.002 – 0.076 mg/L (4 hour). Human cases of acute dermal or inhalation exposure report burning, metallic taste, giddiness, headache, nausea, chest tightness, gastrointestinal upset, dyspnea, parasthesia.
- MMT was also shown to be a mild skin and eye irritant.
- Repeat dose inhalation studies carried out over a period of 30 weeks found that at doses of 0.014 and 0.017 mg/L mice exhibited 26.2% and 35.9% weight loss and 1/10 and 28/28 mortality. Rat exposed to doses of 0.017mg/L MMT exhibited a 10.7% weight loss and 9/20 mortality. The NOAEL for rats and mice is 0.0062 mg/L.
- MMT was found to have no observed adverse effect levels (NOAEL) of 9 and 10 mg/kg bw/day in rat developmental studies.
- The genotoxicity of MMT is overall negative for both *in vitro* and *in vivo* studies. However, NICNAS does note one positive *in vitro* chromosome aberration study.
- The carcinogenicity of MMT could not be determined due to insufficient data, although a negative result was obtained in a single study.
- The NICNAS evaluator indicated that based on public health risk calculations, exposure to a petrol additive product containing MMT through accidental ingestion may represent a significant acute health risk, particularly to children.

On the basis of its toxicological profile and use pattern the NICNAS evaluator recommended that MMT be included in Schedule 7 with a cut-off to Schedule 6 for fuel additive preparations containing 10% or less of MMT when fitted with a child-resistant closure.

A Member expressed concern that inclusion in Schedule 6 for fuel additive preparations would have a significant regulatory impact as most products currently available would not be packaged in Schedule 6 poisons containers. Other Members were confident that companies could produce containers consistent with those stipulated for a Schedule 6 poison and that a spout could also be incorporated to minimise spillage and thus human exposure to MMT during use.

The XXXXXXXXXX evaluator informed the Committee that there had been no known reports of poisonings involving products containing MMT. However, this may be as a result of Poisons Information Centres collecting information on poisoning due to petroleum products in general and not MMT specifically.

A Member noted that the companies producing these products who had provided information to NICNAS for their assessment had not taken the opportunity to make a submission to the NDPSC with regard to the scheduling of MMT. It was suggested that

the proposed scheduling be foreshadowed to allow interested parties to comment prior to a decision being made.

OUTCOME

The Committee agreed to foreshadow the inclusion of MMT in Schedule 7 with a cut-off to Schedule 6 for fuel additive preparations containing 10% or less of MMT when packaged within a container with a pouring spout and fitted with a child-resistant closure. The decision was based on the acute toxicological profile of MMT and that the use pattern of consumer products fitted with a child-resistant closure will limit the exposure direct to the public.

Foreshadowed for consideration at the February 2004 meeting

Schedule 7 – New Entry

METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL **except** when included in Schedule 6.

Schedule 6 – New Entry

METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL in fuel additive preparations containing 10 per cent or less of methylcyclopentadienyl manganese tricarbonyl when fitted with a child-resistant closure.

5.1.3 VIRGINIAMYCIN

PURPOSE

The Committee considered a request seeking the reinstatement of virginiamycin for use in feed additives for horses in Schedule 5.

BACKGROUND

The scheduling of virginiamycin was considered at the February 2003 Meeting and included in Schedule 4 for all uses based on advice received from the Expert Advisory Group on Antimicrobial Resistance (EAGAR). EAGAR advised that continued unrestricted use of virginiamycin posed an unacceptable risk to human health from the development and transfer of organisms resistant to this class of antibiotics in food animals. This scheduling decision was also consistent with the Government response to the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) Recommendation 6. The Schedule 4 amendment came into effect on 1 September 2003.

XXXXXXXXXX markets a feed additive XXXXXXXXXX, which contains 10 g/kg virginiamycin. It is used in conjunction with high grain diets to maintain low blood D-lactate (of gut origin) and to reduce the risk of laminitis. The company sought continued

inclusion of their virginiamycin containing product in Schedule 5 on the basis that treatment of non-food producing animals did not pose a threat to humans through the development of resistant bacterial strains.

DISCUSSION

The Committee was informed that advice from EAGAR regarding the potential for the development of antibiotic resistance resulting from the use of virginiamycin in non-food producing animals had not yet been received. However, the EAGAR assessment report provided for the Committee's consideration at the February 2003 meeting recommended the inclusion of virginiamycin in Schedule 4 for all species.

A Member advised the Committee that the use of virginiamycin for the treatment of laminitis in horses in the United Kingdom is no longer recommended XXXXXXXXXX and that virginiamycin is a prescription only medicine in New Zealand.

The Committee was advised that whilst laminitis is not a reversible condition, the careful feeding of horses was enough to prevent occurrence.

Given that the issue had not been gazetted, the Committee thought it prudent to defer consideration of the use of virginiamycin in non-food producing animals until advice had been received from EAGAR.

OUTCOME

The Committee noted the absence of EAGAR's advice regarding the potential for the development of antibiotic resistant resulting from the use of virginiamycin in non-food producing animals and agreed to defer this agenda item to the February 2004 meeting.

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

6.1 1,2-ETHANEDIAMINE POLYMER WITH (CHLOROMETHYL) OXIRANE AND N-METHYLMETHANAMINE

PURPOSE

The Committee considered the scheduling of the new active constituent - 1,2-ethanediamine polymer with (chloromethyl)oxirane and N-methylmethanamine.

BACKGROUND

XXXXXXXXXX applied for approval of the active ingredient 1,2-ethanediamine polymer with (chloromethyl) oxirane and N-methylmethanamine, to be used as a formulated product to control algae in swimming pools. The product, XXXXXXXXXX,

is a 50% aqueous solution of 1,2-ethanediamine polymer with (chloromethyl) oxirane and N-methylmethanamine (1,2-EDP).

DISCUSSION

Member noted that the inclusion of the polymer in Schedule 6 may not be warranted if aqueous preparations containing greater that 50% of the active could not be prepared. The Committee was subsequently informed that the product was manufactured as a 50% solution and that solutions containing the polymer were unlikely to be prepared at concentrations greater than those used in the toxicological tests. Therefore, the Committee thought it appropriate to include 1,2-ethanediamine polymer with (chloromethyl)oxirane and N-methylmethanamine in Schedule 5.

DECISION 2003/39 - 10

The Committee agreed to include 1,2-ethanediamine polymer with (chloromethyl)oxirane and N-methylmethanamine in Schedule 5 on the basis of the available toxicological data.

Schedule 5 – New Entry

1,2-Ethanediamine polymer with (chloromethyl)oxirane and N-methylmethanamine.

6.2 ETOXAZOLE

PURPOSE

The Committee considered the scheduling of etoxazole.

BACKGROUND

XXXXXXXXXX applied for registration of XXXXXXXXXX, a suspension concentrate containing 110 g/L of etoxazole. Etoxazole is a new XXXXXXXXXX used to control mites in cotton and pome fruit. It acts by inhibiting the moulting process in juvenile mites (eggs, larvae and nymph).

DISCUSSION

Based on the available data CPAS recommended that etoxazole be excluded from poisons scheduling.

The Committee agreed that the low toxicity of the compound warranted exemption from scheduling requirements.

DECISION 2003/39 - 11

The Committee agreed to exempt etoxazole from scheduling on the basis of low toxicity and included it in Appendix B under category 1.2 – insecticide.

Appendix B – New Entry

ETOXAZOLE …….……..October 2003……..……..a……..1.2

6.3 ENDOLSULFAN

PURPOSE

The Committee considered the scheduling of endosulfan (33%) in a microencapsule suspension formulation.

BACKGROUND

Endosulfan is a synthetic dioxathiepin cyclodiene compound used in agriculture to control a range of insects and mites on a broad spectrum of crops. Endosulfan has been available in Australia for over 30 years, and used in the home garden (currently not permitted), commercial food crops and other crops such as cotton. It is currently in Schedule 7 of the SUSDP. During 1970s to 1980s, the chemical was up- and down-scheduled several times between S6 and S7. The Committee, during 1990-1991, considered its high acute toxicity, and maternotoxic and testicular effects after repeated dosing, its availability for home garden use, and recurrent poisoning incidents including fatalities. In November 1990, endosulfan was ultimately rescheduled to S7, and its domestic packs and the S6 entry were cancelled.

By year 2000, there were over 18 end use products of endosulfan with over 400 approved (registered) uses Australia wide. However, in March 2001, registration of ultra low volume (ULV) endosulfan products was cancelled, following restrictions and suspension of the products imposed in June 2000. The actions were initiated by the detection of unacceptable levels of endosulfan residues in beef which had placed Australia's export meat trade at risk. The APVMA then extended the period when the registrations and associated label approvals of all endosulfan products were suspended, to 31 December 2003. The reason for the suspension was that using the products in accordance with some of the label instructions might be an undue hazard to the safety of people and might unduly prejudice trade.

XXXXXXXXXX has submitted data for the registration of a new product XXXXXXXXXX, a microcapsule suspension formulation containing 330 g/L endosulfan. In this product, endosulfan is encapsulated in a polymer shell that limits its bioavailability and hence the toxicity. Endosulfan is slowly released from the polymer shell following application. The product is proposed to be used for the control of heliothis (*Helicoverpa spp.*) and various other insect pests on cotton. No domestic use and food

crop applications are involved. The product is restricted to be supplied to, or used by authorised persons.

DISCUSSION

The toxicology data submitted in support of registration of XXXXXXXXXX were assessed by the OCS. The Committee noted in the toxicology evaluation report prepared by the OCS that:

Based on the extensive data reviewed in 1998 under the APVMA Existing Chemical Review Program, endosulfan is of high acute oral, dermal and inhalation toxicity. It is a slight irritant to rabbit skin, but not an irritant to rabbit eyes, nor a skin sensitiser in guinea pigs. The kidneys and testis appeared the main target organs for endosulfan after repeated dosing in rats, resulting in increased kidney weights, granular pigment formation, progressive chronic glomerulonephrosis or toxic nephropathy, and testicular atrophy. Endosulfan did not show genotoxicity, carcinogenicity, reproduction toxicity and teratogenicity.

[paragraph deleted]

The Committee noted that the reduced acute toxicity of the product was due to the microencapsule formulation, and the toxicology evaluation on the product was consistent with its inclusion in Schedule 6, similar to other encapsulated products such as those containing parathion-methyl or cadusafos. It was noted that the microencapsules were suspended in an aqueous solution containing XXXXXXXXXX. However, concerns remained on the ultimate release of endosulfan, the potential exposure and high toxicity, and its effects on trade. On this ground, a member suggested that all endosulfan products should remain in Schedule 7.

Members were informed by the XXXXXXXXXX representative that while the endosulfan review was initiated by an undue hazard to the safety of people and might unduly prejudice trade, endosulfan is classified as a restricted chemical that can only be supplied to or used by an authorised person and this status would not be affected by the down scheduling of this product.

[paragraph deleted]

Members discussed the potential risk of a microencapsulated “image product” without submission and assessment of toxicology studies on the product. The NDPSC expressed the view that any new microencapsule product containing endosulfan should have chemical and toxicology data submitted to the NDPSC for scheduling consideration.

DECISION 2003/39 - 12

The Committee agreed that on the basis of the reduced acute oral and dermal toxicity, and low topical irritation, microencapsulated endosulfan should be included in Schedule 6 for aqueous preparations containing 33 percent or less of endosulfan.

Schedule 6 - New entry

ENDOSULFAN in aqueous preparations containing 33 per cent or less of microencapsulated endosulfan.

Schedule 7 – Amendment

ENDOSULFAN – amended entry to read:

ENDOSULFAN **except** when included in Schedule 6.

6.4 DELTAMETHRIN

PURPOSE

The Committee considered the scheduling of deltamethrin (11%) in an emulsifiable concentrate formulation.

BACKGROUND

Deltamethrin is a synthetic pyrethroid insecticide. XXXXXXXXXX had applied for the registration of a new product XXXXXXXXXX, containing 110 g/L deltamethrin for use on a variety of field crops, and was seeking a Schedule 6 classification for the product.

Deltamethrin was initially scheduled as Schedule 6 of the SUSDP at the February 1979 Meeting, and was moved to Schedule 7 in May 1979 due to occupational health concern. The S7 classification of deltamethrin was reviewed several times in the following years and ultimately confirmed in November 1988 based on the available acute and chronic toxicity data. XXXXXXXXXX, an aqueous suspension formulation of 1 per cent deltamethrin, in no organic solvent other than a glycol was the first product to be scheduled in S5 which occurred in November 1988. XXXXXXXXXX, containing 2.5 per cent of deltamethrin was included in Schedule 6 in February 1993. Over the years, a wide range of products containing deltamethrin were considered by the Committee for inclusion in S6 or S5.

The Committee considered a 250 g/L SC at the August 1999 meeting. Oral and dermal toxicity was low in rats with LD50s of 5523 mg/kg and >5000mg/kg respectively. Inhalational toxicity was also low with no deaths observed in rats tested at 2300 mg/m^3. There was no skin irritation or sensitisation with the product. Eye irritation was moderate. The Committee acknowledged the acute toxicity profile was consistent with Schedule 5.

However, the Committee remained concerned over the neurotoxic effects of deltamethrin including paraesthesia, and the potential interactions with other pesticides, and concluded that Schedule 6 remained appropriate.

The Committee also considered a 250 g/L WG deltamethrin product at the February 2002 meeting. The oral and dermal toxicity was low in rats with LD50s above 3465 and 2090 mg/kg respectively. Inhalational toxicity was not tested. The product was a slight skin irritant and moderate eye irritant in rabbits and was not a skin sensitiser in guinea pigs. The Committee agreed that, although the acute toxicity profile of 250 g/L WG was appropriate for Schedule 5, the Committee remained concerned of the potential for neurotoxicity and the likely flow-on effects of other deltamethrin products and agreed that the product should be included in Schedule 6.

DISCUSSION

The toxicology data submitted in support of registration of XXXXXXXXXX were assessed by the OCS. The Committee noted the following issues highlighted in the toxicology evaluation report prepared by the OCS:

The toxicity of deltamethrin has been evaluated previously. It is of moderate to high acute oral and inhalation toxicity, but low dermal toxicity. It is a skin irritant and a mild eye irritant in rabbits, but not a skin sensitiser in guinea pigs. It is noted that oral and dermal toxicity varies, depending on the carrier vehicle/solvent. Powder formulations and aqueous suspensions are considerably less toxic than formulations in oils or organic solvents. The oral LD50 in rats varies between 30 mg/kg bw in peanut oil to > 5000 mg/kg bw in aqueous suspension. In humans, paraesthesia is frequently seen after dermal exposure to pyrethroids including deltamethrin, which is a result of a direct effect on intrecutaneous nerve endings.

[paragraphs deleted]

A Member was concerned that specifying the solvent in the formulation in the schedule entry could be disclosure of product information. However, the similar solvent specification for the product formulation of deltamethrin had been shown in the Safety Directions (in the same report), and the sponsor made no comments on it after viewing the report. In fact, information on the concentration, formulation and specific solvents is frequently included in the FAISD.

A Member suggested a more general figure, 12.5% or 15% deltamethrin to be used as the upper limit for this entry. Members noted that the existing Schedule 6 for preparations at 3% or less deltamethrin was set based on pharmacological data. Current toxicology evidence was obtained on an EC formulation containing 10% deltamethrin, and a slight increase to 11% for the product was not considered to significantly affect the toxicity. However, there was no toxicological data to support a further increase of the concentration to 12.5% or 15% deltamethrin without changes in the toxicology profile.

DECISION 2003/39 - 13

The Committee agreed to include deltamethrin in emulsifiable concentrates containing 11% or less of deltamethrin in Schedule 6 of the SUSDP on the basis of reduced acute oral and dermal toxicity. The solvents used in the formulation are specified in the scheduling entry since acute toxicity of deltamethrin is largely related to the carrier vehicle/solvent.

Schedule 6 - Amendment

DELTAMETHRIN – amended entry to read

DELTAMETHRIN:

(a) in aqueous preparations containing 25 per cent or less of deltamethrin, when no organic solvent, other than 10 per cent or less of a glycol, is present;

(b) in wettable granular preparations containing 25 per cent or less of deltamethrin;

(c) in water-dispersible tablets each containing 500 mg or less of deltamethrin;

(d) in emulsifiable concentrates containing 11 per cent or less of deltamethrin in a solvent containing 40 per cent or less of acetophenone and 45 per cent or less of liquid hydrocarbons; or

(e) in other preparations containing 3 per cent or less of deltamethrin,

except when included in Schedule 5.

6.5 ULOCLADIUM OUDEMANSII

PURPOSE

The Committee considered the scheduling of *Ulocladium oudemansii*.

BACKGROUND

XXXXXXXXXX applied for a permit to trial the new microbial product XXXXXXXXXX as a biocontrol against *Botrytis cinerea* infection in grapevines. The active constituent in XXXXXXXXXX is XXXXXXXXXX XXXXXXXXXX XXXXXXXXXX XXXXXXXXXX from XXXXXXXXXX XXXXXXXXXX

XXXXXXXXXX XXXXXXXXXX. *Ulocladium* species occur commonly around the world and have been isolated as saprophytes from soils and the wood, seeds, stems, leaves, and leaf litter of many different plants, as well as from air and water, and cellulose-containing materials such as paper, textiles and building materials. XXXXXXXXXX is supplied as a liquid spore suspension that is diluted 1/100 (1% solution) with water prior to spraying.

U. oudemansii has yet to be found in Australia, though other species of *Ulocladium* have been identified in most states.

DISCUSSION

Based on the available data CPAS recommended that *U. oudemansii* XXXXXXXXXX be exempt from scheduling on the basis that it exhibited low toxicity.

A Member raised a concern regarding the apparent contradiction in the statements that "the genus *Ulocladium* is reported to be a common airway allergen" and "however, it is likely to have low inhalational toxicity". The Committee was advised that for a particle to be inhaled into the lungs its size needed to be consistently below 10 μm. A member advised that given that the *U. oudemansii* spore size is larger (length 18-34 μm and width of 10-17 μm) they would be regarded as not being inhalable.

DECISION 2003/39 - 14

The Committee agreed to exempt *Ulocladium oudemansii* from scheduling on the basis of low toxicity and included it in Appendix B under category 1.10 – biological control agent.

Appendix B – New Entry

ULOCLADIUM OUDEMANSII……..…….October 2003…….…a…….…1.10

6.6 NAPHTHALENE

PURPOSE

The Committee considered the scheduling of naphthalene.

BACKGROUND

XXXXXXXXXX submitted an application to vary the label of an existing registered product, XXXXXXXXXX, consisting of 990 g/kg of naphthalene, for use as a moth repellent in wardrobes, clothes drawers and for the protection of books and other paper or cloth based material in storage.

XXXXXXXXXX would be used to deter moths, silverfish and other insects from eating clothing, books and other paper or cloth items. The label indicates that flakes should be scattered throughout storage areas to deter moths and silverfish. Label advice also includes to place the flakes in envelopes or between sheets of paper to prevent staining of treated materials.

DISCUSSION

The Committee noted the following points raised in the CPAS evaluation report for consideration:

- Naphthalene is readily absorbed when inhaled, or administered orally or dermally, and readily passes the placenta into the foetus.
- In rats naphthalene has exhibited low oral and dermal toxicity (oral LD50 490 and 1100 - 9430 mg/kg bw, dermal > 2500 mg/kg bw) but has moderate inhalational toxicity (8 hr LC50 500 mg/m^3). Mice are more sensitive with the oral LD50 reported in the range 350-710 mg/kg bw. In rabbits naphthalene is a slight eye and skin irritant. Naphthalene is not a skin sensitiser in a number of guinea pig studies but in sensitised individuals, produces severe dermatitis and is a skin irritant in normal persons. Occupational ocular exposure to naphthalene dust has been reported to cause corneal irritation and injury, with cataracts forming after prolonged exposure. The lowest lethal doses reported in humans are 100 mg/kg bw in a child and 29 and 74 mg/kg in adults.
- Chronic abuse of naphthalene by sniffing causes peripheral neuropathy, chronic renal failure and liver necrosis.
- CPAS has suggested the following warning statement be included in the FAISD Handbook, and should be included on the product label for all naphthalene products used in the home.

"Do not use on the clothing of infants or in the bedrooms of young children."

The CPAS assessment concluded that the two principal hazards associated with naphthalene use in domestic environments are haemolytic anaemia, particularly in young children, and particular where they are G6PD deficient, and potential carcinogenicity.

Based on the available data CPAS recommended that the existing poison scheduling for naphthalene remained appropriate. The Committee was asked to consider adding the above warning statement to Appendix F of the SUSDP.

A member expressed concern that the label change resulting from this additional warning statement would have a significant regulatory impact. It was proposed that the APVMA consult with registrants to assess the possible regulatory impact and report to the February 2004 Meeting.

A Member raised the issue of whether an appropriate definition for young children was available. The Committee agreed to request that the CPAS evaluator present more information on the exposure studies referred to in the evaluation, including the ages of children involved, the study location and publication date. This information is to be provided for the next meeting so that an appropriate age range for children can be defined. The Committee agreed to defer their consideration of this matter to the February 2004 Meeting.

OUTCOME

The Committee agreed to defer this matter to the February 2004 Meeting.

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

7.1 HOME GARDEN PRODUCTS – PACK SIZES

PURPOSE

The Committee considered the proposal to include a pack size limit for home garden pesticides in the SUSDP.

BACKGROUND

The APVMA labelling code limits the pack sizes of home garden products to an upper size limit of approximately 1 litre or 1 kilogram. However, some products, such as ready to use products, have been allowed to exceed this restriction.

Larger pack sizes in and around the home were likely to increase the potential of an accidental poisoning occurring through opened and unused chemical product being stored in the home for longer periods of time.

Advice obtained by the APVMA suggested that the upper size limit of their labelling code may not be enforceable thus making it difficult to control pack sizes should the applicant wish to market products in quantities above 1 litre/kilogram to home garden chemical users. As a consequence, the APVMA's labelling code may not provide adequate protection to the public should the applicant challenge a decision based on these principles. The NDPSC was asked to consider this issue and an amendment to Part 3 of the SUSDP.

DISCUSSION

The Committee was advised that the proposed amendment to Part 3 to restrict home garden products to 1 kg or 1 L may not be successful as not all jurisdictions adopt this part of the SUSDP into their own poisons legislation.

A member proposed that the jurisdictions consult with their departments which administer control of agricultural and veterinary chemical use legislation to determine whether home garden pack sizes could be limited to 1 kg or 1 L through State and Territory legislation and report to the February 2004 Meeting. In addition, the Committee agreed that the APVMA should determine whether the trend toward larger home garden pack sizes was significant enough an issue to warrant the inclusion of restrictions in the SUSDP.

OUTCOME

The Committee agreed to defer consideration of this issue to the February 2004 Meeting.

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

BACKGROUND

In 1999, the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) recommended:

"That all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)" (Recommendation 6).

The Commonwealth Government's response to the JETACAR Report accepted "the concept that all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)". However, the Government's acceptance was qualified by highlighting that "… certain antibiotic products might be exempted from this scheduling class where the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA) and the NDPSC assess the antibiotic products as having a low and acceptable risk of promoting antibiotic resistance".

The Committee agreed at the June 2002 Meeting that the scheduling of antibiotics currently registered with the APVMA, but not separately listed in the SUSDP would be reviewed at the June 2003 meeting. This intention was included in the post - October 2002 meeting notice published in the Commonwealth of Australia Gazette No GN 49, 11 December 2002.

The Committee agreed to consider each substance gazetted for consideration at the October 2003 meeting individually. These were: avilamycin (8.1), bambermycin (8.2) and olaquindox (8.3). Additionally, the Committee also agreed to consider the following substances deferred from the June 2003 meeting: cefadroxil (8.4), penethamate hydriodide (8.5) and phthalylsulfathiazole (8.6); and correspondence received concerning tylosin (8.6) and naladixic acid (8.8).

8.1 AVILAMYCIN

PURPOSE

The Committee considered the scheduling of avilamycin.

BACKGROUND

Avilamycin is an antibacterial used in veterinary medicine as a growth promoter. XXXXXXXXXX markets one avilamycin product: XXXXXXXXXX XXXXXXXXXX (100g/kg avilamycin) which is used as a feed productivity enhancer in the production of broiler chickens.

Avilamycin was first considered in November 1986. At the time, XXXXXXXXXX referred the matter to XXXXXXXXXX for further information. In 1998, the NDPSC included avilamycin in Schedule 4 of the SUSDP for all uses except when in animal feed premixes containing 15 % or less avilamycin or 50 mg/kg or less avilamycin activity.

XXXXXXXXXX made a submission in which it recommended that the current use pattern of avilamycin in Australia be retained. The company stated that avilamycin was not currently used as a human antibiotic and was unlikely to be, given the toxicity problems associated with the human clinical use of everninomicins. XXXXXXXXXX considered that until such a time as a human clinical dossier is presented for regulator approval, there was no medical or scientific justification to alter the current usage practices of avilamycin in Australia. Furthermore, XXXXXXXXXX held the view that in the unlikely event that an antibiotic from this class was presented for registration for human use, it was confident that its non-human use could be halted and an avilamycin susceptible enterococcal population restored in chickens prior to the introduction of the human drug.

In a further submission, XXXXXXXXXX stated that the risk of antibiotic resistance transfer for avilamycin was negligible and that there were sufficient industry controls in place to ensure that use of the product was controlled, prudent and consistent with a risk management strategy that would further minimise the risk of resistance transfer.

DISCUSSION

The Committee was informed that that submission from XXXXXXXXXX was referred to EAGAR for assessment. Members noted advice received from EAGAR which recommended that the current scheduling status of avilamycin not be changed on the basis that:

- Everninomicins were not currently used in human medicine due to toxicity.
- There was no evidence that avilamycin promoted co-resistance (it does not exert selective pressure for VRE in animals).

- It has a low and acceptable risk of promoting antibiotic resistance (in humans).
- The lower concentrations are classified, as 'not scheduled' based on lesser toxicity not the potential to select for resistance.

The Committee also noted advice received from the APVMA in which it stated that, as there are no human drugs currently containing avilamycin, the use of this antibiotic in animal production was considered to pose minimal risk in promoting antibiotic resistance.

OUTCOME

The Committee agreed that the current scheduling status of avilamycin remained appropriate.

8.2 BAMBERMYCIN (FLAVOPHOSPHOLIPOL)

PURPOSE

The Committee considered the scheduling of bambermycin (flavophospholipol).

BACKGROUND

Bambermycin (flavophospholipol) is an antibacterial used in veterinary medicine as a growth promoter. Currently there are four registered products containing bambermycin. XXXXXXXXXX markets three products: XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX while XXXXXXXXXX markets XXXXXXXXXX.

Bambermycin (flavophospholipol) was first considered by the Committee in 1978 and included in Schedule 4 of the SUSDP for all uses except when in schedule 6 (in animal feed premixes at 2% or less), in animal feed premixes containing 50 mg/kg active antibiotic principle or in milk replacements and pig starter rations containing 100 mg/kg or of the antibiotic principle. In 1998 the current scheduling entry was amended with reference to flavophospholipol being deleted from the SUSDP.

DISCUSSION

The Committee was informed that XXXXXXXXXX made a public submission in which it stated that the current scheduling of bambermycin was appropriate and should be retained. The company made the point that development of resistance to bambermycin has not been reliably proven. By contrast, the company claimed that bambermycin has been repeatedly shown to reduce resistance plasmid transfer rates between *E. coli, S. tyhimurium and Enterococci*. The company concluded that rescheduling bambermycin in Schedule 4 for all uses would greatly reduce the benefits of this substance to animal production industries, the consumer and the environment.

The Committee was informed that that submission from XXXXXXXXXX was referred to EAGAR for assessment. Members noted advice from EAGAR recommending that the

current scheduling status of bambermycin remained appropriate on the basis that scheduling at lower concentrations (≤ 2% or ≤ 50 mg/kg) was related to toxicity rather than antimicrobial resistance and that this class of antimicrobial was not used in human medicine.

OUTCOME

The Committee agreed that the current scheduling status of bambermycin remained appropriate.

8.3 OLAQUINDOX

PURPOSE

The Committee considered the scheduling of olaquindox.

BACKGROUND

Olaquindox is an antibacterial used in veterinary medicine as a growth promoter. Currently there are three registered products containing Olaquindox. XXXXXXXXXX markets two products: XXXXXXXXXX and XXXXXXXXXX XXXXXXXXXX markets XXXXXXXXXX.

Olaquindox was first considered by the Committee in 1976 and included in Schedule 6 of the SUSDP.

DISCUSSION

The Committee was informed that public submissions were received from XXXXXXXXXX and XXXXXXXXXX.

XXXXXXXXXX stated that olaquindox is of great benefit in the production of pig meat because it improves growth rate, improves feed efficiency, reduces the incidence of scours and is effective in the control and treatment of campylobacter infections. Furthermore, while a small number of farm labourers working with products containing olaquindox have experienced photo allergy and photo toxicity, no known adverse reactions have been observed in XXXXXXXXXX employees.

XXXXXXXXXX advised that it was not aware of any major livestock company, intergrator or farmer within their sphere of influence who was adding olaquindox to feeds without veterinary advice or prescription. Therefore in its opinion, the rescheduling of olaquindox to Schedule 4 for all uses would have little impact on its use. The company felt that the methods by which the feed was prepared and presented were of greater importance to the issue of antibiotic resistance rather than the availability of the antibiotic.

The Committee was informed that these submissions were referred to EAGAR for assessment. Members noted advice from EAGAR which recommended that the current Schedule 6 classification for olaquindox was acceptable. This was on the basis that there were no human antibiotics related to this substance currently in use and as such its continued veterinary use was unlikely to affect treatment outcomes for bacterial disease in humans. In addition, the infections in animals targeted by olaquindox use were important from an economic and animal welfare perspective. Availability of olaquindox for pig production was likely to discourage use of other drugs having far greater bearing on the management of resistance in human pathogens, such as tylosin.

The Committee also noted that the APVMA had advised the use of olaquindox in animal production was considered to pose minimal risk for promoting antibiotic resistance on the basis that there are no human drugs currently containing the substance.

A member expressed concern over the findings of a Danish study (Sorensen *et al., Antimicrob Agents Chemother.* 2003, **47**,798) which identified a transferable plasmid in *E. coli* from pig manure that encoded for resistance to olaquindox, ampicillin and chloramphenicol. The member suggested that this may be the first indication of a larger problem with the use of olaquindox in pig production. The Committee was advised that the APVMA conducts monitoring of post-registration data on the trends of antibiotic resistance and that this program would identify an increased incidence of resistance, leading to a review of the product. The Committee agreed to request that EAGAR update the NDPSC in 2 years on any other examples of antibiotic resistance development as highlighted in the Danish study.

OUTCOME

The Committee agreed that the current scheduling status of olaquindox remained appropriate. It was further agreed to request that EAGAR update the Committee in 2 years on any other examples of antibiotic resistance development as highlighted in the Danish study.

8.4 CEFADROXIL

PURPOSE

The Committee considered the scheduling of cefadroxil.

BACKGROUND

Cefadroxil is an antibacterial used in the treatment of susceptible infections due to group A streptococci, staphylococci, *S. pneumoniae*, *H. influenzae*, Klebsiella species, *E. coli* and *P. mirabilis*, and for the treatment of impetigo, pharyngitis/tonsillitis, skin/skin structure infections and urinary tract infections. In veterinary medicine cefadroxil is used to treat infections caused by susceptible gram positive and gram negative bacteria in dogs and cats.

The scheduling of cefadroxil was to be considered at the June 2003 Meeting but was deferred to the October 2003 Meeting due to the absence of the expected EAGAR assessment report.

DISCUSSION

The Committee noted advice received from EAGAR that recommended all preparations containing cefadroxil be included in Schedule 4 because of the capacity to select for resistance to first-generation cephalosporins and a range of other unrelated antibiotics.

The Committee was advised that there was currently an entry for cefadroxil in Schedule 4 under an alternative spelling - cephadroxil. Accordingly, the Committee agreed to amend the Schedule 4 entry to reflect the INN.

DECISION 2003/39 - 15

The Committee agreed to amend Schedule 4 entry for cefadroxil to reflect the INN spelling.

Schedule 4 - Amendment

CEPHADROXIL – amend entry to read:

CEFADROXIL

8.5 PENETHAMATE HYDRIODIDE

PURPOSE

The Committee considered the scheduling of penethamate hydriodide.

BACKGROUND

Penethamate hydriodide is a penicillin antibacterial used in veterinary medicine for the treatment of susceptible infections caused by gram positive bacteria, such as mastitis, uterine infections, respiratory infections and foot rot in cows, horses, sows and sheep.

The scheduling of penethamate hydriodide was to be considered at the June 2003 Meeting but was deferred to the October 2003 Meeting due to the absence of the expected EAGAR assessment report.

DISCUSSION

The Committee noted interim advice received from EAGAR that supported an entry for penethamate hydriodide in Schedule 4.

A Member advised the Committee that salts of substances were usually excluded for scheduling entries and that including penethamate hydriodide in Schedule 4 would be contrary to this policy. It was proposed that penethamate rather than penethamate hydriodide be included in Schedule 4.

DECISION 2003/39 - 16

The Committee agreed to include penethamate in Schedule 4 for all uses.

Schedule 4 – New Entry

PENETHAMATE.

8.6 PHTHALYLSULFATHIAZOLE

PURPOSE

The Committee considered the scheduling of phthalylsulfathiazole.

BACKGROUND

Phthalylsulfathiazole is an antibacterial used in veterinary medicine for the treatment of gastrointestinal infections in dogs and cats.

Phthalylsulfathiazole was included in the list of substances to be reviewed under EAGAR on the basis that it was not listed in the SUSDP. However, it was included under Phthalylsulphathiazole in Schedule 4 at the November 1998 Meeting.

DISCUSSION

The Committee agreed to maintain the focus of its considerations on the issue of antibiotic resistance rather than the spelling of individual schedule entries. Accordingly, the Committee agreed that the current scheduling status of phthalylsulphathiazole remained appropriate and that its Schedule 4 entry be amended to reflect its INN spelling.

DECISION 2003/39 – 17

The Committee agreed that the current scheduling status of phthalylsulfathiazole remained appropriate. It was further agreed to amend the phthalylsulfathiazole entry in Schedule 4 to reflect its INN spelling.

Schedule 4 - Amendment

PHTHALYLSULPHATHIAZOLE – amend to read:

PHTHALYLSULFATHIAZOLE.

8.7 TYLOSIN

PURPOSE

The Committee considered correspondence from XXXXXXXXXX in regard to the antibiotic scheduling review under JETACAR.

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 posed 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.

This decision to include virginiamycin in Schedule 4 for all uses was confirmed at the June 2003 Meeting. XXXXXXXXXX believed that the rescheduling of virginiamycin prior to other veterinary antibiotics currently outside Schedule 4 could result in the non-S4 antibiotics being used in place of virginiamycin to avoid the cost of engaging a veterinarian. It was claimed that this would have undesirable consequences for animal health and welfare as well as undesirable impacts on food residues and transfer of antibiotic resistance. XXXXXXXXXX requested that the NDPSC consider harmonising the effective date for the re-scheduling of all animal use antibiotics.

XXXXXXXXXX submitted to the Committee correspondence from XXXXXXXXXX to feed mill sales representatives promoting unapproved claims for a registered product containing tylosin.

DISCUSSION

The Committee noted that XXXXXXXXXX letter highlighted the NDPSC's decision regarding the rescheduling of virginiamycin to Schedule 4 and reminded sales representatives that their product, XXXXXXXXXX (tylosin) had been unaffected by the scheduling decision and remained in Schedule 5. XXXXXXXXXX was of the view that advertising of this type was clearly contrary to the Government intent of placing antibiotic use under the control of veterinarians to provide additional surety of prudent use. The company conceded that there was little that the NDPSC could do regarding this issue, however, proposed that the Committee consider the issue in the broader context as an opportunity for future process improvement.

The Committee was advised that tylosin was not included in the NDPSC's antibiotic scheduling review timetable because it was being considered by the APVMA under JETACAR Recommendation 2.

Members understood that the APVMA reconsideration is currently in the assessment phase and it is expected the NDPSC would consider the public health assessment of this substance in due course.

A member informed the Committee that a decision was made at the beginning of the review process that the NDPSC should not try and proceed independently of the reviews being undertaken by the APVMA so as to avoid an uncoordinated approach or duplication.

A member proposed that claims of inappropriate promotion of antibiotics which were yet to be reviewed by the NDPSC be referred to EAGAR and the APVMA.

OUTCOME

The Committee agreed to refer claims of inappropriate promotion of antibiotics that are yet to be reviewed under JETACAR to EAGAR and the APVMA.

8.8 NALIDIXIC ACID

PURPOSE

The Committee noted the EAGAR report for nalidixic acid.

BACKGROUND

The rescheduling of nalidixic acid was considered by the Committee under JETACAR recommendation 6 at the February 2003 Meeting. At the time EAGAR was unable to provide a completed assessment report for nalidixic acid but it provided an interim recommendation that the substance be included in Schedule 4 for all uses on the basis that it belongs to an important therapeutic class in human medicine. The Committee has endorsed EAGAR's recommendation and agreed to include nalidixic acid for all uses in Schedule 4 of the SUSDP which was consistent with the Government response to JETACAR Recommendation 6. This recommendation came into effect on 1 September 2003.

DISCUSSION

Members were provided with the EAGAR final assessment for nalidixic acid which confirmed its interim advice to the February 2003 Meeting.

OUTCOME

The Committee noted the EAGAR report for nalidixic acid.

PHARMACEUTICALS

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

12.1 LEVONORGESTREL

PURPOSE

The Committee considered post-meeting submissions in relation to the June 2003 initial decision to reschedule levonorgestrel in a two-tablet pack, of 0.75 mg per tablet, for emergency post-coital contraception from Schedule 4 to Schedule 3 of the SUSDP.

BACKGROUND

The June 2003 Meeting considered the scheduling of levonorgestrel for emergency contraception (EC). The Committee agreed to include levonorgestrel in a two-tablet pack, of 0.75 mg per tablet, for emergency post-coital contraception in Schedule 3 of the SUSDP. The decision was based on established safety and efficacy of the product, the need for timely access and its OTC availability in several countries for a number of years. Additionally, the distributor's undertaking to provide appropriate training and educational materials to aid pharmacists in giving professional advice and counselling to consumers on the safe and effective use of this product was taken into account. An Appendix H listing for levonorgestrel was also proposed but was not considered by the Committee due to insufficient information.

DISCUSSION

Members noted that a large number of post-meeting submissions were received. Some submissions were from those who did not make a pre –meeting submission and therefore, did not comply with regulation 42ZCZ of the Therapeutic Goods Regulations 1990. Nonetheless, the Committee agreed to consider all submissions received for this item. The submissions are summarised in Attachment 2.

The Committee noted that XXXXXXXXXX, XXXXXXXXXX, the XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX supported the decision. It was submitted that women in both the metropolitan and rural (including remote) areas would benefit from the decision, and it may lead to reduced abortion rates. However, the additional endeavours including education, monitoring programs, inclusion of advice on methods of ongoing contraception, access to testing for sexually transmitted diseases (STDs) and recommended medical review to exclude ongoing pregnancy in the Product Information had been suggested. The sponsor committed to ensuring the provision of adequate training and educational materials for pharmacists, including advice about the risk of ectopic pregnancy, adverse effects and potential needs for medical management.

The Committee considered the arguments opposing the rescheduling proposal contained in the post-meeting submissions from several professional groups and the general public. Almost without exception, the issues raised in the June 2003 post-meeting submissions had been dealt with at the June 2003 meeting. The following issues were again raised in the post-meeting submissions received and the Committee considered information that should allay concerns about these issues:

The perceived abortifacient action and legal liability of pharmacists
Levonorgestrel is not considered by the Committee to be an abortifacient. This view was determined by the TGA at the time of registration of XXXXXXXXXX and would not be changed by the rescheduling of levonorgestrel for EC from S4 to S3. The legal implications of a pharmacist providing levonorgestrel EC were considered to be no different to the supply of any other S3 product. One post-meeting respondent suggested that by supplying levonorgestrel EC directly, ie. without a prescription, a pharmacist could be "procuring a miscarriage" which would be a criminal offence. In the Committee's view, a pharmacist could only be "procuring a miscarriage" if they were supplying an agent deemed to be an abortifacient, which levonorgestrel is not.

Concerns about toxicity and contraindications
The Committee noted that worldwide post-marketing surveillance that covered over 15 million uses of the product has not (with the exception of ectopic pregnancies) identified any new or emergent adverse events. WHO considers only unexplained vaginal bleeding, current breast cancer, pregnancy and hypersensitivity to levonorgestrel to be absolute contraindications. All can be assessed using history taking by pharmacists rather than specific diagnostic tests or medical examination. Pharmacists are already well trained in the techniques of appropriate questioning prior to supply of S3 substances. The risks and consequent need for doctor monitoring associated with long-term ongoing use of oral contraceptives (minipills at S4) are quite different to those associated with a single use of two 0.75 mg tablets of levonorgestrel. For example, thromboembolism is more likely linked to ongoing exposure than the brief, albeit higher dose of this product (< 0.03% with levonorgestrel as EC). The oestrogen content in contraception products is mainly responsible for the risk of thromboembolism. Most women presenting for levonorgestrel emergency contraception are likely to be otherwise healthy and relatively young. The potential for serious adverse events to occur with levonorgestrel emergency contraception is low and less of a public health issue than the adverse events and social problems associated with both abortion and unwanted pregnancies.

Concerns about the risk of ectopic pregnancy
Spontaneous reports to the XXXXXXXXXX in the UK and XXXXXXXXXX indicated that use of levonorgestrel EC may be associated with a very small increase in incidence

of ectopic pregnancy. It is now advised by XXXXXXXXXX and XXXXXXXXXX that any woman who does not have a menstrual period within the expected time frame or has abnormal bleeding or pelvic pain after taking levonorgestrel EC, should seek medical advice. This advice can be adequately conveyed to the consumer.

Concerns on existing pregnancy and potential teratogenesis
The WHO document entitled "Emergency Contraception: A guide for service delivery" directs providers to exclude the possibility of pregnancy by establishing the date and nature of the last menstrual period and establishing the time of the first and last episodes of unprotected intercourse since the last menstrual period. Other assessments such as laboratory tests and pelvic examination are unnecessary unless the answers to the questions about menstrual period and sexual intercourse indicate that current pregnancy is possible. Similar to any other S3 product where use in pregnancy is not advised, pharmacists would be able to question the client appropriately to determine the chance of pregnancy. If the pharmacist has any doubt as to whether the woman may be pregnant they can refuse to supply the drug and refer the woman to a doctor.

A pregnancy which occurs as a result of failure of the levonorgestrel emergency contraception would not be at risk. The half-life of levonorgestrel is approximately 24 hours, and levels are likely to be undetectable 5 days after taking the dose. Since implantation usually occurs 7-10 days after ovulation, the likelihood of exposure of the developing baby to levonorgestrel is quite remote. With respect to teratogenicity, the product information for XXXXXXXXXX makes it quite clear that based on previous experience with combined oral contraceptives, an increase in congenital abnormalities would not be expected except where levonorgestrel is administered at or after eight weeks post-conception. This use would be outside the registered indications.

Some of those who made submissions referred to a 1975 paper by Nora and Nora which described a collection of congenital anomalies known as the VACTERL syndrome. Although a few women in this paper were treated with a progestagen alone (medroxyprogesterone in a 10 mg dose), most were treated with combined oestrogen/progestagen and of the 19 patients whose babies were born with the VACTERL anomalies, 6 were not treated with any hormonal agents and of the 13 who were, 3 had taken other potential teratogens as well. Members were of the view that this study was too small and the confidence intervals too wide for any real conclusions about teratogenicity from progestagen exposure to be drawn. Also of note was the fact that more recent publications including the product information documents for XXXXXXXXXX made no mention of this syndrome.

Concerns about waiving of the "2 year rule"
Levonorgestrel has been available OTC in other similar countries, e.g. the UK and France, for at least 2 years, and by prescription in the UK and USA for longer. Furthermore, two doses of 25 tablets each of the 30 microgram levonorgestrel "XXXXXXXXXX" had been used "off label" by a number of doctors and Family Planning Clinics for emergency contraception prior to the formal marketing of XXXXXXXXXX. The actual clinical use of levonorgestrel EC in Australia is longer than the period of availability of XXXXXXXXXX, and on this ground, waiving of the 2-year rule is reasonable.

Concerns about potential drug interactions
Pharmacists are experienced in counselling about drug interactions and counselling about interactions with levonorgestrel EC is no different. All the potential interactions listed are not that levonorgestrel affects the drug already being taken but the opposite: that the levonorgestrel may be less effective mainly due to decreases in levonorgestrel levels due to hepatic enzyme induction. All the drugs listed in the Product Information for XXXXXXXXXX as potential interactions would meet the Schedule 3 criterion of being commonly used drugs or foods.

Concerns about repeated use and potential use as an ongoing form of contraception
Specific clinical trial data was presented at the June 2003 meeting which addressed both these concerns. The two main arguments presented in June indicating that repeated use of levonorgestrel EC is unlikely to be attractive still stand: firstly, side-effects such as nausea and interruption of the menstrual cycle are likely to be barriers and secondly, levonorgestrel EC is less efficacious than other ongoing contraceptive methods. It was shown by the data that pharmacy availability in the UK had resulted in increased usage of levonorgestrel EC, which might have only reflected better availability of levonorgestrel EC (the very thing that moving to S3 is trying to achieve) rather than increased sexual promiscuity. A study performed in Ghana by Lovvorn and others (2000) reported that "Our data did not suggest that the availability of EPCs increased the frequency of unprotected intercourse". Similarly, a controlled study of 263 women who presented to a family planning clinic in San Francisco also found that advance provision of emergency contraception did not result in reports of higher frequencies of unprotected sexual intercourse (Raine et al 2000). On the other hand, provision on prescription does not preclude the possibility of a woman deliberately seeking repeated use of levonorgestrel EC by going to different doctors or different hospital emergency departments, or obtaining a prescription for XXXXXXXXXX with multiple repeats, as has repeatedly occurred.

Concerns about risk of missing the chance to test for sexually transmitted diseases (STDs)
Pharmacists can be trained to counsel appropriately about the need for STDs screening depending on the woman's circumstances. Material already developed in the UK lists specific questions which pharmacists can use in this situation. Also of note is that for some STDs, e.g. Hepatitis B and C and HIV/AIDS, an immediate blood test is inappropriate and the patient will still have to make another visit to the doctor or remember to go to a pathology laboratory 3 months later to be adequately tested.

Concerns that availability on prescription has not been shown to reduce abortion rates
Abortion rates are influenced by many factors including the legislative environment of the country where they are being measured. The reasons why abortion rates alone may not be the best measure of the public health benefit of wider availability of levonorgestrel EC were well elucidated at the June 2003 meeting.

Concerns about lack of privacy and training for consultation in pharmacies The manufacturer has committed to ensuring that training materials and other materials such as those developed in the UK will be readily available to pharmacists. In some states, the relevant pharmacy organisations are already well on the way to developing training programs and materials for use by pharmacists who may be asked to provide levonorgestrel EC. Regarding lack of privacy in pharmacies, a woman still has the option of visiting her doctor for a prescription, if she is concerned about the lack of privacy in a pharmacy. All the methods suggested by XXXXXXXXXX to encourage timely access of levonorgestrel EC as a S4 drug, such as advance prescriptions, dispensing following a telephone call with a written prescription to follow and emergency medical appointments, are already available yet do not appear to be well known or well utilised.

Concerns about supply to patients under 16 years of age
Members noted that the cut-off age for supply was mentioned by several correspondents, and both medical and legal arguments were presented opposing supply by pharmacists to those under 16 years. The product information for XXXXXXXXXX does suggest that data in the 14 and 16 year age group is limited. In the UK, supply by pharmacists directly is limited to females 16 years or over. Members were also informed that the legislation in Queensland prevented pharmacists from providing S3 medicines to people under the age of 16 years, except when such medicines were sought under a doctor's prescription. Pharmacists may recommend that any woman under 16 years seeking levonorgestrel should go to a doctor for a prescription, or call from the pharmacy for a doctor's appointment. This would be a matter of professional judgment based on each individual circumstance.

Inclusion in Appendix H
The Committee confirmed the view taken out the June 2003 Meeting that an Appendix H listing for levonorgestrel was not warranted due to insufficient information available to support an informed decision about advertising.

Overall the Committee reiterated that levonorgestrel EC in a dose of 2 x 0.75 mg tablets clearly conforms to the criteria for a Schedule 3 medicine both in terms of the characteristics of the drug and the indications for use. The main reason for rescheduling to Schedule 3 is to provide timely access to the substance remembering that 95% of expected pregnancies are prevented if levonorgestrel emergency contraception is taken within 24 hours of unprotected intercourse, 85% if it is taken between 24 and 48 hours and only 58% if it is taken between 48 and 72 hours.

DECISION 2003/39 – 18-Confirmation of Amendment (Decision 2003/38 – 25)

In accordance with subregulation 42ZCZ(3), the Committee confirmed the amendment (Decision 2003/38-25) made at the June 2003 meeting, with minor editorial changes, to include levonorgestrel in a two tablet pack, of 0.75 mg per tablets, for emergency post-coital contraception in Schedule 3 of the SUSDP. The decision was based on the following:

- Enabling timely access to levonorgestrel for EC to achieve high efficacy.
- A well-established safety profile in terms of toxicity, contraindications and drug interactions.
- Levonorgestrel for EC use has been available in several countries for a number of years including use as a non-prescription product.
- The product satisfies the criteria for Schedule 3 listing.
- The sponsor commits to provide appropriate training and educational materials for pharmacists.
- The pharmacist is required to provide professional advice and counselling to consumers to ensure that the product is used safely and effectively.

Schedule 3 - New entry

LEVONORGESTREL in tablets each containing 0.75 mg of levonorgestrel, in a primary pack containing two such tablets, for emergency post-coital contraception.

Schedule 4 - Amendment

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

12.2 IBUPROFEN

PURPOSE

The Committee considered further public submissions in relation to June 2003 decision to exempt small packs of ibuprofen from scheduling.

BACKGROUND

2. The June 2003 NDPSC Meeting made an initial decision to exempt from scheduling divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 25 or less dosage units when labelled with a recommended maximum daily dose of 1200 mg of ibuprofen. The decision was based on the Committee's opinion 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 of 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.

DISCUSSION

Members noted that a large number of post-meeting submissions were received (Attachment 3). Some submissions were from those who did not make a pre –meeting submission and therefore, did not comply with regulation 42ZCZ of the Therapeutic Goods Regulations 1990. Nonetheless, the Committee agreed to consider all submissions received up to 17 September 2003 for this item.

The consideration commenced with a presentation by an expert member who had reviewed in detail the submitted references. The Committee discussed the following points raised in post-meeting submissions opposing the decision to exempt low dose ibuprofen from scheduling.

Concerns about the PAIN study
The Committee noted that several submissions enclosed or quoted an article recently published in Australian Pharmacist by Professor Gregory Peterson (University of Tasmania) regarding the PAIN study referred to in the sponsor's submission. The PAIN study was a large randomised clinical trial investigating the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. XXXXXXXXXX expressed doubt on the methodology and hence the strength of evidence presented in the PAIN study on which he believed the down-scheduling decision was based. He pointed out that the published paper did not include comprehensive inclusion and, in particular, exclusion criteria for patients included in the study.

A copy of the final clinical trial report for the PAIN study, which contained more details than the published version, had been obtained by the Secretariat and reviewed by an expert member. It was noted that the exclusion criteria in the PAIN study were essentially the contra-indications associated with ibuprofen, aspirin and paracetamol, which included gastrointestinal ulcer, pregnancy or lactation, allergy to NSAIDs and severe asthma. Members were of the view that it seemed probable that the cohorts studied in the PAIN Study were similar to those who would take appropriately ibuprofen purchased on unrestricted sale. It was noted that the contraindications and precautions associated with the use of ibuprofen were to be covered by appropriate labelling of the small packs.

The Committee noted that after excluding patients with a history of upper gastrointestinal ulcer in the PAIN study, the incidence of drug-induced abdominal pain and dyspepsia

was lower in the ibuprofen-treated group than with other groups. On this basis, it was reasonable to conclude that based on the findings of the PAIN study, low dose ibuprofen for intermittent and short term use had a better gastrointestinal safety profile compared to aspirin and paracetamol for the same use.

Concerns on gastrointestinal complications
The Committee noted that several submissions expressed concern on the potential gastrointestinal (GI) complications induced by ibuprofen. The FDA report (Memorandum from RA Bonnel et al, 2002) referred to by XXXXXXXXXX, reviewed 197 cases of GI bleeds, ulceration or perforation reported for over-the-counter NSAIDs in the US during 1998-2001, including 105 cases for ibuprofen. FDA reviewers concluded that the patients in the study were at increased risk for GI bleeding in the setting of a past GI event, other significant inter-current illness or past medical history, consumption of alcohol, tobacco use or use of another OTC or prescription medication concomitantly. The expert member noted that the FDA report did not include a reference to the denominator of exposure during the specified time and therefore, a true incidence of GI events could not be determined for this OTC use. Furthermore, another reference provided by XXXXXXXXXX (McCarthy et al 1999) which estimated the risk of adverse events in patients using various classical NSAIDs based on outcome studies of large databases suggested ibuprofen to be considerably safer in terms of upper GI complications compared to other NSAIDs including aspirin, naproxen, diclofenac, piroxicam and ketoprofen.

The Committee agreed that any potential gastrointestinal complications could be covered by an appropriate warning statement.

Concerns about the elderly users and potential risks.
Members noted that although the majority of users of unscheduled analgesics would be healthy individuals aged under 50, based on the sponsor's claim which was accepted by the NDPSC, there would be a population of users at or over 65 years. Several submissions expressed their concerns on the potential risks for ibuprofen use in this sub-population given its side effects and contraindications.

The Committee noted information cited by XXXXXXXXXX and XXXXXXXXXX (from Newspoll survey) that "nearly a quarter of a million Australian could potentially take low-dose aspirin and ibuprofen together". The Committee also noted information cited by XXXXXXXXXX (from survey of pharmacists) that 1% of the total pharmacy response had reported intervention by the pharmacist in a requested sale of ibuprofen to someone already taking low-dose aspirin. The Committee noted that concern about the possible interference of ibuprofen with the cardioprotective effects of low-dose aspirin was based on a study of the effects of cyclooxygenase inhibitors on antiplatelet effects of aspirin (Catella-Lawson et al, NEJM, 2001) and a study of clinical events using a clinical record database (MacDonald TM, Wei L. Lancet 2003). In this latter study, the patients had had their medication supplied by a hospital system and may have been taking ibuprofen long term. Members indicated that it was not possible to draw firm conclusions relevant to the general sale of ibuprofen from this study as there was a lack

of information on doses and duration of treatment with ibuprofen, and no adjustment for severity of diseases and other risk factors (e.g. smoking) was made for each treated group.

Members were of the view that although long term use of ibuprofen might interact with the cardioprotective effects of low-dose aspirin, this effect was unlikely to be a significant concern with short term use of low dose ibuprofen based on available information. The Committee decided that inclusion of a precautionary statement relating to use of ibuprofen in elderly patients, such as "Unless a doctor has told you to, don't use this product if you are taking other medicines containing aspirin or other anti-inflammatory medicines or other medicines you are taking regularly" would reduce possible risks associated with self-administration of ibuprofen in patients taking low dose aspirin.

Concerns on women users and the risk of miscarriage

The Committee noted that several post-meeting submissions mentioned the findings of a cohort study conducted in the US and published in the British Medical Journal (Li et al 2003), which suggested an increase in relative risk for miscarriage in users of NSAIDs. The cohort study was based on interviews of 1055 pregnant women recruited immediately after confirmation of pregnancy, about the use of NSAIDs, aspirin and paracetamol. The paper did not provide an analysis for each of the NSAID used by the subjects in the study except aspirin, and had the limitation of being a *post hoc* analysis of a study originally designed to assess the prenatal exposure to magnetic fields. Whilst it was noted that the cohort study concluded that paracetamol had no effect on the risk of miscarriage, members' attention was drawn to an early finding of a heightened risk of spontaneous abortion or foetal death in paracetamol overdose during pregnancy (Riggs et al, Obstet Gynaecol 1989).

Based on available information, there was no compelling evidence to suggest that ibuprofen was associated with a higher incidence of miscarriage compared to other NSAIDs. However, the Committee agreed that it was appropriate to include a precaution not to use ibuprofen if pregnant on the product label.

Concerns on NSAIDs-related renal failure ("triple whammy")

Members discussed the potential risk of drug-related renal failure associated with the use of NSAIDs together with ACE inhibitors and/or diuretics. Some recent Australian data (ADRAC, 1990-2002) were provided. These indicated that the number of reported cases of renal failure implicated with 1). ibuprofen alone, 2). Ibuprofen and ACE inhibitor or diuretic, or 3). Ibuprofen, ACE inhibitor and diuretics represented only 3-4% of the total reports of renal failure attributed to all NSAIDs, alone or in combination. While great caution was needed to interpret spontaneous reports data it was suggested that ibuprofen showed fewer reported adverse renal effects compared to other NSAIDs.

The XXXXXXXXXX representative expressed concern that the Committee was down-playing the importance of the ADRAC reports of renal failure and was potentially

showing a lack of consistency in decision-making. The Committee considered that these concerns would be addressed through appropriate labelling.

NSAIDs-induced asthma
Members were aware of the concerns on NSAIDs-induced asthma by several respondents. Similar to that for aspirin, a warning statement for NSAID-induced asthma was already proposed for ibuprofen products.

Concerns on the pack size of the product
XXXXXXXXXX claimed that 25-dose forms representing a 4-day treatment was an excessive pack size for open sale ibuprofen. However, XXXXXXXXXX did not provide any evidence to support the safety concern raised with the 25-tablet (5 g ibuprofen) pack size, which the Committee noted was equivalent to the pack size of general sale aspirin (7.5 g) and paracetamol (12.5 g). On this basis, the Committee agreed that the pack size limit of 25 tablets (total of 5 g ibuprofen) remained appropriate.

Consultation to doctors / pharmacists
Several pharmacy organisations raised the issue that use of ibuprofen required pharmacist consultation, given the potential side effects. The Committee noted that the current S2 classification did not require intervention by a pharmacist in each sale. The Committee also noted that the potential side effects associated with short-term use of ibuprofen would be dealt with in the warning statements that would be required for general sale products. In addition, the Committee emphasised that a decision to exempt a product from scheduling does not preclude the sale of such a product in pharmacies where access to a pharmacist is available to consumers.

Current availability
Ibuprofen in divided preparations containing 200 mg or less of ibuprofen per dosage unit in a pack containing 50 or less dosage units and labelled with a recommended daily dose of 1200 mg or less of ibuprofen was included in Schedule 2 (S2) in May 1995. S2 means that pharmacist intervention is not mandatory at the point-of-sale, and that the request for advice is initiated by the purchaser. During this period of S2 availability, no significant safety issues were submitted to the Committee. In addition, a member advised that ibuprofen was an S2 product in NSW, which was allowed to be sold in country stores without pharmacists, and this had not given rise to major adverse cases being reported.

Consistency with other NSAIDs in scheduling
The Committee confirmed that ibuprofen was a NSAID with a good safety record that was comparable to paracetamol and better than aspirin, particularly, in relation to gastrointestinal events. Although paracetamol was generally considered as the first line analgesic agent, ibuprofen was safer than paracetamol in overdose, due to the hepatotoxicity associated with paracetamol overdose.

The Committee concluded that there was sufficient evidence to support the exemption from scheduling requirements of intermittent low dose and short-term use of ibuprofen, provided that appropriate warning statements were included on the product label.

DECISION 2003/39 – 19 - Variation of Amendment (Decision 2003/38 – 23)

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary the amendment (Decision 2003/38-23) made at the June 2003 meeting 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, by amending the label Warning Statements.

The decision was based on the following reasons:

- The indications for low dose (≤1200 mg/day) oral administration of ibuprofen are suitable for self-identification and treatment without professional advice.
- Ibuprofen has a comparable safety profile to existing unscheduled analgesic products (aspirin and paracetamol in small pack sizes) indicated for the same use.
- Ibuprofen products have been available for general sale in the USA since 1984, and in the UK since 1996 with no significant safety issues arising over that time, and there is considerable OTC marketing experience in Australia as an S2 medicine.
- Ibuprofen has a wide therapeutic index, and the risk of masking a serious disease is very low.
- Appropriate warning statements for GI complications, pregnancy, asthma and use in certain age groups have been included to reduce the risks in sensitive sub-populations.
- Ibuprofen has a very low to absent potential for abuse.

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 a 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; and

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

Don't use [this product / name of the product]:
If you have a stomach ulcer
In the last 3 months of pregnancy [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea*]
If you are allergic to ibuprofen or other anti-inflammatory medicines; and

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 or other medicines that you are taking regularly
If you have asthma
In children 6 years of age or less
If you are aged 65 years or over
If you are pregnant [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea*].

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.

12.3 TERIPARATIDE

PURPOSE

The Committee considered post-meeting comment relating to the June 2003 meeting recommendation to include the new medicine, teriparatide, in Schedule 4 (S4) of the SUSDP.

BACKGROUND

Teriparatide is a recombinant human parathyroid preparation XXXXXXXXXX.

DISCUSSION

Members advised that a mechanism was in place in the jurisdictions where patients in remote areas with no immediate access to specialists could obtain on-going prescriptions through a GP under the direction of a specialist.

DECISION 2003/39 – 20 - Variation to Amendment (Decision 2003/38-31)

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary the amendment (Decision 2003/38-31) made at the June 2003 meeting to include teriparatide in paragraph 1 of Appendix D for public health and safety reasons. The Committee was of the view that inclusion in Appendix D would put in place additional controls on supply and availability in addition to Schedule 4 to ensure that the 18-month total lifetime treatment limit was not exceeded and thereby minimise the potential risk of osteosarcoma.

Schedule 4 – New entry

TERIPARATIDE.

Appendix D, Paragraph 1 – New entry

TERIPARATIDE for human use.

12.4 FLUCONAZOLE

PURPOSE

The Committee considered the inclusion of fluconazole in Appendix H.

BACKGROUND

The June 2003 Meeting considered the rescheduling of fluconazole. The Committee agreed to include fluconazole in Schedule 3 for single-dose oral preparations containing 150 mg for the treatment of vaginal candidiasis. The decision was made on the basis of its similar safety profile to topically applied antifungal agents, and was considered appropriate for similar S3 availability.

DISCUSSION

The Committee noted that the sponsor XXXXXXXXXX made a post-meeting submission seeking approval to advertise fluconazole 150 mg single dose when included in Schedule 3 of the SUSDP, with the following main points:

- Fluconazole has high efficacy as a single-dose treatment for vaginal candidiasis and a favourable safety profile. Its OTC availability should have the advantage of patient preference and improved compliance.
- Brand advertising would alert women to the fact that there is an oral alternative to topical drug therapy available for the treatment of thrush.
- Advertising would allow women to make a choice of therapy (in consultation with the pharmacist), which best suits their needs with respect to rapidity of relief of symptoms and convenience.
- Advertising would be expected to raise the level of consumer knowledge about vaginal candidiasis.
- OTC advertising would direct women to health professionals who are able to provide the best advice on the condition and treatment options, and who can direct the women to a doctor if required.
- The likelihood of advertising leading to inappropriate patterns of medication use is low.

Members noted the following points highlighted in the expert's assessment on the Appendix H inclusion of the substance:

- Comparable vaginally applied treatments for the same condition are permitted to be advertised, and alerting women to the availability of an alternative orally administered product could be considered a useful public health message.

- The sponsor committed to adhere to the Therapeutic Goods Advertising Code, to include the importance of initial medical diagnosis and the pharmacists' counselling role, and provide CMI and other material needed to educate product users.
- Low potential for advertising to promote inappropriate use.

The Committee noted that MEC had recommended (Item 8.1 of the October 2003 MEC Meeting) that Appendix F Warning Statement No 64 (ie. "See a doctor if no better after three days") be include on the labels of Schedule 3 fluconazole products. A period of "three days" was set as the vaginal mucosa would not necessarily have recovered earlier than this after a single dose fluconazole treatment.

In addition, it was noted that XXXXXXXXXX considered fluconazole to be a valuable first line treatment which could be life-saving when used for the treatment of cryptococcal infections, particularly in AIDS patients. After extensive discussion, the Committee was of the view that it was unlikely for resistance to develop with fluconazole given the treatment of vaginal candidiasis comprises of a single and discrete oral dose of fluconazole.

The Committee also agreed to include fluconazole in Appendix H when it was included in Schedule 3, given that there should be reinforcement through appropriate advertising that the product was recommended as a second-line treatment for vaginal candidiasis after the failure of a topical antifungal.

DECISION 2003/39 – 21 - Variation to Amendment (Decision 2003/38-29)

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary the amendment (Decision 2003/38-29) made at the June 2003 meeting to include fluconazole in Appendix F and Appendix H of the SUSDP. The decision at the June 2003 meeting to include fluconazole in single-dose oral preparation containing 150 mg or less of fluconazole for the treatment of vaginal candidiasis in Schedule 3 was made on the basis of comparable safety profile to other topical azole products for the same indication. Inclusion in Appendix F (Warning Statement 64) and Appendix H was also consistent with other Schedule 3 imidazole antifungals for vaginal use.

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.

Appendix F, Part 3 – New Entry

Fluconazole
Warning Statement …… 64

Appendix H – New Entry

Fluconazole

13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

13.1 SILICONES

PURPOSE

The Committee considered an amendment to the Appendix C entry for silicones foreshadowed at 38th (June 2003) Meeting.

BACKGROUND

During the consolidation of SUSDP No.17, many inconsistencies and editorial errors were discovered. One such inconsistency was the silicones entry in Appendix C. The Committee agreed, at Meeting 38, to change the Appendix C entry for silicone by adding the words "or implantation" to provide consistency within the SUSDP and to reflect the original intent of the Committee at the time that the entry was made.

DISCUSSION

The Committee was advised that the proposed amendment was included in the Pre-October 2003 gazette notice and was returned to the Committee for finalisation. No public submissions in relation to this matter were received.

Members confirmed the foreshadowed amendment.

DECISION 2003/39 - 22

The Committee agreed to modify the Appendix C entry for silicones as foreshadowed at Meeting 38.

APPENDIX C – Amendment

SILICONES – amend entry to read:

SILICONES for tissue augmentation by injection or implantation.

13.2 PSEUDOEPHEDRINE

PURPOSE

The Committee continued its consideration of the scheduling of undivided, combination and slow release preparations of pseudoephedrine in Schedule 2.

BACKGROUND

The June 2002 Meeting agreed to reschedule all OTC single-active immediate release pseudoephedrine preparations from Schedule 2 to Schedule 3, and foreshadowed the consideration of scheduling of S2 pseudoephedrine formulations at the October 2002 NDPSC 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 by XXXXXXXXXX, and for sponsors to indicate their plans for existing and future product lines.

The February 2003 Meeting and the June 2003 agreed to defer further consideration of the scheduling of undivided, combination and slow release (SR) pseudoephedrine preparations in Schedule 2 to allow more time to review the findings of XXXXXXXXXX investigation. This was specifically the extractability of pseudoephedrine from various OTC formulations and agreed to defer any further scheduling until the October meeting. It was considered prudent 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

DISCUSSION

The Committee noted pre- October 2003 meeting comment was received from XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX which supported the present scheduling requirements for pseudoephedrine. Additionally, pre-meeting comment from XXXXXXXXXX requested the right to make a post-meeting submission on any recommendations made on pseudoephedrine. Also members were informed that XXXXXXXXXX has issued a draft determination for the "*Code of Conduct - Helping Prevent the Diversion of Non-Prescription Medicines Containing Pseudoephedrine*" for a period of 5 years.

Advice from XXXXXXXXXX member indicated that the National Working Group on the Diversion of Precursor Chemicals (NWG) research and its analysis were, to date, not finalised.

Members were informed that the NWG that met on 26 June 2003 provided funding for the analytical research and that initial results from other research undertaken to date indicate extraction of pseudoephedrine from multiple component pharmaceutical preparations via liquid-liquid extraction is relatively uncomplicated and an average recovery of 78% is achievable.

The Committee discussed recent police action which uncovered approximately 7000 tablets in a vehicle in XXXXXXXXXX. It suggested that this finding may not necessarily indicate that pharmacists are becoming less vigilant in observing anomalous purchasing behaviour with pseudoephedrine in Schedule 3.

The Committee believed that single active preparations of pseudoephedrine were most likely the problem with diversion to the illicit drug trade.

As the NWG analytical report was not available discussion was held on whether the research findings would be sufficient to proceed with any scheduling action, it was suggested that this may be pre-empting the NWG if this was undertaken. The industry representative advised that previous discussions with the XXXXXXXXXX on pseudoephedrine revealed that they perceived no scheduling changes were warranted at this stage.

The XXXXXXXXXX representative noted that pharmacists were being advised by their representative organisations of any actions recommended with illicit drugs within a few days of Health Department recommendations.

It was agreed that the Secretariat prepare a letter for XXXXXXXXXX asking that the NDPSC be advised by January 30 2004 of any NWG outcomes so that it can be reported and considered at the February 2004 meeting.

OUTCOME

The committee agreed to:

- defer any further scheduling action until the February 2004 meeting to allow consideration of the outcomes of the extraction research and other measures agreed to by the National Working Group; and,
- carry over all public submissions for pseudoephedrine from previous meetings.

13.4 MITRAGYNINE

PURPOSE

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

BACKGROUND

Mitragynine (also known as Kratom) is one of the alkaloids found in the leaves of the South-East Asian tree *Mitragyna speciosa*, which is used extensively in Thailand to increase work output and tolerance of direct sunlight. Mitragynine has psychoactive properties and has been associated with being used as an opium substitute. Kratom leaves are usually chewed, smoked or drunk as tea to achieve the desired affect. *Mitragyna speciosa* is regulated in the same way as cocaine and heroin in Thailand and carries the same restrictions and penalties as cocaine. There have also been reports of use of mitragynine in Malaysia. Poisindex indicates that in adults, a dose of 50 mg of pure mitragynine has produced motor excitement, rombergism, giddiness and tremors of the face, extremities and tongue. In 1975, a study of 30 Thai Kratom users considered chronic (more than 5 years use) noted that the leaves were chewed three times to 10 times a day, with stimulant effects occurring after five minutes to 10 minutes.

The February 2003 Meeting considered preliminary information in relation to mitragynine and M*itragyna speciosa*. This consideration was initiated by an inquiry to the TGA from an Australian resident wishing to import mitragynine and concern regarding its potential for abuse. Members discussed the pharmacology and toxicology of mitragynine, its potential for abuse, and the potential impact of its inclusion in the SUSDP. The Committee agreed that there were grounds for inclusion of mitragynine and M*itragyna speciosa* in the SUSDP, based on mitragynine's mode of action. To allow appropriate public consultation, the Committee agreed to foreshadow the inclusion of mitragynine and M*itragyna speciosa* in Schedule 9 of the SUSDP, for consideration at the June 2003 meeting.

The June 2003 Meeting noted the studies which showed that mitragynine exerted agonistic effects on opioid receptors in *in-vitro* studies as well as an antinociceptive action, which suggested that mitragynine has a morphine-like action on gastric acid secretion. A member pointed out that tramadol is a mu-opioid receptor agonist included in S4 and that it has a low potential for producing dependence. Members noted that the information from Poisindex (Micromedex Healthcare) indicated that addiction and withdrawal symptoms had occurred with chronic use of M*itragyna speciosa*. The Committee subsequently agreed to defer further consideration of the foreshadowed decision on the view that additional information was required to better characterise the physiological effects and mechanisms of action of mitragynine.

DISCUSSION

The Committee noted the advice received from XXXXXXXXXX stating that it had not seen conclusive evidence relating to abuse or misuse of *Mitragyna speciosa* or mitragynine. XXXXXXXXXX submitted that evidence on addiction and other harms seen with *Mitragyna speciosa* or mitragynine had been largely anecdotal, and in some instances contradictory. XXXXXXXXXX was of the view that given the range of psychoactive substances being advertised on internet web sites, the limited user base and the nature of use, it was unlikely that abuse of *Mitragyna speciosa* would become widespread in Australia.

The Committee noted the literature review of pharmacological and toxicological data on mitragynine prepared by the Secretariat. Animal experiments with mitragynine had shown that it possessed pain threshold-elevating and antitussive properties. A series of pharmacological studies in animal models, *in vivo* and *in vitro*, indicated that similar to morphine, mitragynine and its derivatives produced central antinociception, inhibition of intrinsic activity or electrically elicited guinea pig ileum contraction and drug-induced gastric acid secretion, and inhibition of cAMP content. It was demonstrated in receptor binding studies that these effects were mediated by opioid receptors and that further studies also indicated that the pharmacological actions of mitragynine were selectively blocked by antagonists for some sub-types of opioid receptors, predominantly mu- and delta-receptor subtypes. (*Matsumoto et al, Eur J Pharmacol 1996; Thongpradichote et al, Life Sciences 1998; Tohda et al, Biological & Pharmaceutical Bulletin 1997; Tsuchiya et al, Eur J Pharmacol 2002; Takayama et al, J Med Chem 2002; Yamanoto et al, General Pharmacol 1999*).

Based on available data, members noted that habitual users of mitragynine could develop marked withdrawal syndromes, including hostility, aggression, rhinitis, inability to work, excess tears, muscle and bone aches and jerky limb movement. Members concurred with the view that there was a strong possibility of addiction if mitragynine was used in doses high enough for mu-receptor crossover (*1974-2003 Thomson Micromedex. Micromedex(R) Healthcare Series Vol. 115)* and agreed to restrict the use of the substance.

Members discussed whether similar restrictions should be imposed on the plant species, *Mitragyna speciosa,* in the light of reports that the leaves of the plant were being used for smoking and chewing, and the leaf extracts drank as tea, to achieve the 'desired' effects. A member also raised the issue that there was a possibility that the plant was being used for ornamental purposes and that the Committee should defer confirmation of the foreshadowed decision to the next meeting to allow further information to be sought on this matter.

DECISION 2003/39 – 23

The Committee agreed to take a pro-active approach and included mitragynine in Schedule 9 of the SUSDP based on its potential for abuse. The Committee recognised

that whilst there were no widespread reports of abuse of mitragynine in Australia at this time, the information relating to the use of mitragynine for psychoactive effects, particularly in Asian countries, was well documented and easily found on the internet.

Schedule 9 – New Entry

MITRAGYNINE.

OUTCOME

The Committee agreed to consider the foreshadowed inclusion of the plant species, *Mitragyna speciosa,* in S9 of the SUSDP at the February 2004 to seek additional information on the plant's uses.

Foreshadow for consideration at the February 2004 meeting

Schedule 9 – New entry

MITRAGYNA SPECIOSA.

13.5 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'.

XXXXXXXXXX received a complaint regarding a treatment described as "chemobrasion" which is a form of chemical skin peeling. The applicant alleged that following application of a 20% TCA solution by an enrolled nurse, the consumer was left with injuries attributed to the procedure and has since undergone remedial treatment. XXXXXXXXXX also received a subsequent unconfirmed report that beauty therapists were also applying TCA. The XXXXXXXXXX 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.

The 38th (June 2003) NDPSC considered this matter and 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 2003 gazette notice.

DISCUSSION

The Committee noted that no public submissions were received.

It was recalled that the 38th (June 2003) meeting noted an extemporaneous preparation Upton's Paste 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.

Members noted that the concentration of trichloroacetic acid in Upton's Paste was greater than 10% and agreed to exempt wart preparations at a maximum concentration of 12.5%.

DECISION 2003/39 - 24

The Committee agreed to include trichloroacetic acid for dermal use in Schedule 4 of the SUSDP and the subsequent amendment to the Schedule 6 entry for trichloroacetic acid on public health and safety grounds. The Committee was of a view that that inclusion of the substance in Schedule 4 except preparations containing 12.5% or less for wart removal except for the treatment of warts (other than anogenital warts) should significantly reduce the potential for inappropriate use of the substance.

Schedule 4 – New entry

TRICHLOROACETIC ACID for human dermal use **except** when in preparations containing 12.5 per cent or less of trichloroacetic acid for the treatment of warts other than anogenital warts.

Schedule 6 – Amend entry

TRICHLOROACETIC ACID – amend entry to read

TRICHLOROACETIC ACID **except**:

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

(b) in human dermal preparations containing 12.5 per cent or less of trichloroacetic acid for the treatment of warts other than anogenital warts.

13.6 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.

The 38th (June 2003) NDPSC meeting considered the scheduling of memantine and noted that in New Zealand memantine is classified as a prescription medicine.

In order to meet the statutory requirements the Committee agreed to foreshadow, for consideration at the October 2003 meeting, the inclusion of memantine in Schedule 4 of the SUSDP.

DISCUSSION

The Committee noted that while animal studies have reported adverse effects of memantine on the visual system, no conclusive evidence of ocular toxicity in the clinical setting was observed.

XXXXXXXXXX advised that the ADEC methodology of assessment is based on the European assessment methodology on statistical significance and not clinical significance and that it comes before the NDPSC after it was registered following a successful appeal to ADEC.

DECISION 2003/39 - 25

The Committee agreed to a new entry in Schedule 4 of the SUSDP for memantine on the basis that it is used to treat a medical condition that requires professional medical diagnosis, management and monitoring for side effects; and to harmonise scheduling with New Zealand.

Schedule 4 – New entry

MEMANTINE.

13.7 REVIEW OF NON-PRESCRIPTION ANALGESICS

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) analgesics for inclusion in Appendix F of the SUSDP.

This item is related to substances and items discussed at items 1.8.1.3.2 Paracetamol, 1.8.1.3.3 Aspirin and 12.2 Ibuprofen, and also the sub items referred to below.

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.

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.

The 38th (June 2003) meeting was provided with a copy of the Review of Non-prescription Analgesics – An update, April 2003 (April 2003 Update). Members noted that 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) related to labelling requirements for analgesics that are required by the SUSDP. Additionally, members were aware that the responsibility for regulating label-warning statements was to be transferred from the NDPSC to the TGA in July 2005. The MEC had asked the NDPSC to implement OTC analgesic warning statement changes in the interim period. Members understood that the MEC's proposed package of warning statements for inclusion in Appendix F of the SUSDP are intended to replace the current SUSDP Appendix F warning statements for non-prescription analgesics, except for WS 36 with respect to aspirin.

Gazettal of the proposed MEC warning statements prior to the 38th NDPSC meeting resulted in a number of public submissions being received. The MEC considered these public submissions and provided advice and revised wording to the June 2003 meeting. It was pointed out that the public had not had the opportunity to comment on the revised wording recommended by the June 2003 MEC meeting and accordingly, the Committee agreed that it would not be able to resolve this issue at that meeting and referred the revised changes back to the MEC to enable it to undertake consultation with industry and provide a unified response to the NDPSC for consideration at the October 2003 meeting.

DISCUSSION

The Committee noted that MEC considered the June 2003 NDPSC recommendation at its August 2003 meeting. MEC's response to the NDPSC response including recommended analgesic warning statements was provided to members.

Members were informed that all pre-October 2003 meeting public submissions relating to this matter had been referred to MEC for comment. Public submissions were received from XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX.

MEC considered these public submissions at its October 2003 meeting and a summary of the considerations is at Attachment 4. The issues addressed by MEC were discussed by the Committee.

The XXXXXXXXXX member was concerned about the reasons for adopting the analgesic WS in Appendix F at this time when the TGA was going to transfer warning statements for medicines from the SUSDP to a labelling order in the near future. The Chair advised that inclusion in the SUSDP would allow earlier implementation of the WS and a seamless transition to the new labelling order.

The Committee noted that a number of pre-meeting respondents sought a 12 month transition time to allow time for labels to be updated.

The XXXXXXXXXX member raised the issue that the NDPSC decision, if adopted at this meeting, would require changes to be implemented at State and Territory level by 1 May 2004. It was suggested that there be an additional 12 month transition to allow the changes to come into effect as of 1 May 2005 to avoid undue industry hardship.

The XXXXXXXXXX representative also advised that companies were concerned with statements that were prescriptive by the TGA as opposed to words that carried the same intent. Members discussed the proposition of using performance based labelling as proposed by XXXXXXXXXX.

The Committee noted the pre-meeting submission from XXXXXXXXXX which was concerned with the lack of precision in the proposed warning statement 102, "*Unless a doctor has told you don't take this [medicine] for more than a few days at a time"* but accepted that there was no better alternative. Another pre-meeting submission considered that the current statement on XXXXXXXXXX of "*Do not exceed the recommended dose or use for more than 48 hours without seeking medical advice*", adequately meets the intention of the new recommendations, is more restrictive and better promotes safe use. The NDPSC noted the view of the MEC that the new statement is consistent with this one, therefore the NDPSC proposed no change to revised warning statement 98.

Members noted that some public submissions raised concerns that warning statement 99 may be alarmist and considers that performance testing of the statement may be appropriate before inclusion and the use of the word 'overdose'.

XXXXXXXXXX advised that performance based labelling was a matter for the TGA and the new Trans Tasman Therapeutic Products Regulatory Agency.

OUTCOME

The Committee agreed to transitional arrangements for implementing the new analgesic warning statements, which would come into effect on 1 May 2005. See Items 13.7.1 Paracetamol; 13.7.2 Aspirin; 13.7.3 Ibuprofen; 13.7.4 Naproxen and 13.7.5 Mefenamic acid for specific decisions.

13.7.1 PARACETAMOL

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) paracetamol for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee discussed the concerns raised in public submissions about the inclusion of the PIC phone number in the proposed new warning statement number 99. Members agreed to include the Appendix E section regarding PIC in the introduction section of Appendix F to allow some flexibility.

DECISION 2003/39 - 26

The Committee agreed to the inclusion of the MEC proposed new label warning statements for paracetamol in Appendix F the SUSDP and the consequential amendments to the Schedule 2 entry for paracetamol. It was also agreed that the effective date would be 1 May 2005.

SCHEDULE 2 – AMENDMENT

PARACETAMOL – amend entry to read:

PARACETAMOL for therapeutic use **except**:

(a) when included in Schedule 4;

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

(i) in a primary pack containing not more than 12 such powders or sachets;

(ii) (A) labelled with the statement (permitted until 30 April 2005):

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; or

(B) labelled with the statements (mandatory from 1 May 2005):

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; and

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

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

(i) packed in blister or strip packaging or in containers with child-resistant closures;

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

(iii) (A) the primary pack is labelled with the statement (permitted until 30 April 2005):

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; or

(B) labelled with the statements (mandatory from 1 May 2005):

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; and

(iv) not labelled for the treatment of children 6 years of age or less.

APPENDIX F, INTRODUCTION – NEW ENTRY

Poisons Information Centre Telephone Numbers

Companies should use the poisons information centre telephone number(s) appropriate to the country(ies) of sale for the product, that is Australia or New Zealand or both. These

are 13 1126 for Australia and 03 4747 000 for New Zealand. A new free-call number (0800 764 766) is being introduced in New Zealand. Use of the old number (03 4747 000) shall be phased out by May 2005.

Companies wishing to use a poisons information centre telephone number other than the national telephone numbers for Australia and New Zealand in warning statement No. 99 in Part 1 of this Appendix must meet the following criteria:

1. The poisons information service whose number is used must be attended by adequately trained staff for 24 hour emergency poisons information; and

2. Calls must be logged and submitted for incorporation into the official collection of poisoning data.

APPENDIX F, PART 1 – NEW ENTRIES

97. *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.

98. *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.

99. 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.

100. Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.

APPENDIX F, PART 3 – AMENDMENT

Paracetamol – amend entry to read:

Paracetamol (a)	34 or 35 (permitted until 30 April 2005) or
(b).....	97 and/or 98, 99, 100 (mandatory from 1 May 2005)

13.7.2 ASPIRIN

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) aspirin for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee discussed the overlap between the two pregnancy warning statements as raised by XXXXXXXXXX. Members noted that MEC had advised that both warnings are appropriate as the warning statement *"Don't use this product in the last 3 months of pregnancy"* is a contraindication while the other warning statement *"Unless a doctor has told you to, don't use this product if you are pregnant"* is a caution.

The XXXXXXXXXX member was of the view that the proposed pregnancy warning statements may be 'diluting' the message on pregnancy contained in the relevant analgesic consumer medicine information leaflets.

DECISION 2003/39 - 27

The Committee agreed to the inclusion of the MEC proposed label warning statements for aspirin in Appendix F of the SUSDP and to the consequential amendment to the Schedule 2 for aspirin (this can be found under Item 1.8.1.3.3). It was also agreed that the effective date would be 1 May 2005.

Appendix F, Part 1 - Warning Statements – New Entry

101. Don't use [this product / name of the product]:
If you have a stomach ulcer
In the last 3 months of pregnancy *[This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea]*
If you are allergic to (name of substance) or anti-inflammatory medicines.

102. Unless a doctor has told you to, don't use [This statement 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.

103. See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. *[This statement may be omitted in products for inhibition of platelet aggregation or with additional active ingredients.]*

APPENDIX F, PART 3 – AMENDMENT

Aspirin – Amend entry to read:

Aspirin	
(a) for inhibition of platelet aggregation.	36
(b) in sustained release preparations containing 650 mg or more of aspirin.	36
(c) except as above.	.....(i) 37 and 38 and
	.....(ii) 34 or 35 or 36 (permitted until 30 April 2005) or
	.....(iii) 101, 102, 103 and 37 (mandatory from 1 May 2005)

13.7.3 IBUPROFEN

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) ibuprofen for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee considered that the issues concerning the MEC proposed warning statements raised under the general item 13.7 “Review of non-prescription analgesics” and its sub-items 13.7.1 “Paracetamol” and 13.7.2 “Aspirin” as well as under item 12.2 “Ibuprofen” had allowed for adequate discussion.

DECISION 2003/39 - 28

The Committee agreed to the inclusion of the MEC proposed label warning statements for ibuprofen in Appendix F of the SUSDP. It was also agreed that the effective date would be 1 May 2005.

APPENDIX F, PART 1 – NEW ENTRY

104. 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 (name of substance) or other anti-inflammatory medicines
If you have asthma
If you are pregnant *[This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea]*.

APPENDIX F, PART 3 – AMENDMENT

Ibuprofen – amend entry to read:

Ibuprofen (a)	34 or 35, 71 (permitted until 30 April 2005) or
(b)	101, 104 (mandatory from 1 May 2005)

13.7.4 NAPROXEN

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) naproxen for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee considered that the issues concerning the MEC proposed warning statements raised under the general item 13.7 "Review of non-prescription analgesics" and its sub-items 13.7.1 "Paracetamol" and 13.7.2 "Aspirin" had allowed for adequate discussion.

DECISION 2003/39 – 29

The Committee agreed to the inclusion of the MEC proposed label warning statements in Appendix F of the SUSDP. It was also agreed that the effective date would be 1 May 2005.

APPENDIX F, PART 3 – AMENDMENT

Naproxen – amend entry to read:

Naproxen

(a)	in preparations for the treatment of dysmenorrhoea	(i) 34 or 35 (permitted until 30 April 2005); or (ii) 101, 104 (mandatory from 1 May 2005).
(b)	in other preparations;	(i) 34 or 35, 71 (permitted until 30 April 2005); or (ii) (101, 104 (mandatory from 1 May 2005).

13.7.5 MEFENAMIC ACID

PURPOSE

The Committee considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter (OTC) mefenamic acid for inclusion in Appendix F of the SUSDP.

BACKGROUND

See Item 13.7 Review of non-prescription analgesics.

DISCUSSION

The Committee considered that the issues concerning the MEC proposed warning statements raised under the general item 13.7 “Review of non-prescription analgesics” and its sub-items 13.7.1 “Paracetamol” and 13.7.2 “Aspirin had allowed for adequate discussion.

DECISION 2003/39 - 30

The Committee agreed to the inclusion of the MEC proposed label warning statements for mefenamic acid in Appendix F of the SUSDP. It was also agreed that the effective date would be 1 May 2005.

APPENDIX F, PART 3 – AMENDMENT

Mefanamic acid – amend entry to read:

Mefanamic acid (a)	34 or 35 (permitted until 30 April 2005) or
(b)	101, 104 (mandatory from 1 May 2005)

13.8 IBUPROFEN

PURPOSE

The Committee discussed the MEC request to clarify the rationale behind the current proposal to revise the AGRD 2 guideline for ibuprofen to restrict concentrations of oral liquid ibuprofen preparations in Australia to 100mg/5mL or 200mg/5mL.

BACKGROUND

The November 2000 TTHWP meeting made a recommendation (33/7) that NZ MOH adopt the revised wording of the SUSDP amendment for ibuprofen that sets an upper daily dose for divided and undivided preparations for ibuprofen; and relaxes the concentration requirements for ibuprofen liquid preparations, but retains a 4g total content of ibuprofen in these packs.

The February 2001 NDPSC meeting endorsed this recommendation and referred it to NZ Medsafe. In May 2002 MCC considered TTHWP recommendation 33/7 and agreed that:

- the maximum daily dose for pharmacy-only solid dose and liquid ibuprofen should not exceed 1200 milligrams.
- the maximum pack size for pharmacy-only liquid preparations should not exceed 4g of total ibuprofen content.
- packs of undivided preparations for pharmacy-only sale should be in concentrations only of 100mg in 5ml or 200mg in 5ml of ibuprofen
- That the NDPSC adopt the MCC recommendation limiting the concentrations of liquid ibuprofen permitted in pharmacy-only (S2) medicines.

The May 2002 MCC meeting minutes stated that the purpose of reclassifying liquid ibuprofen to pharmacy-only medicine is to allow for paediatric doses that are not intended for chronic use.

The October 2002 NDPSC meeting agreed to gazette the consideration of scheduling of ibuprofen for consideration at the February 2003 meeting which received pre-meeting comment that objected to the inclusion of a dose limit for the Schedule 2 entry for ibuprofen. This was made on the basis that New Zealand has included the dose limit for ibuprofen in the NZ regulatory guidelines and not in the First Schedule to the NZ Medicines Regulations. XXXXXXXXXX felt it is more appropriate to include this level of detail in the Australian guidelines for the registration of medicines (AGRD vol 2). This approach is considered consistent with the current paracetamol guideline in the AGRD.

The Committee noted that there was harmonisation on pack size. New Zealand, however, had adopted dose limitations into their regulatory guidelines and NZ MCC were recommending harmonisation on strengths. Accordingly, the Committee agreed that the Schedule 2 entry for ibuprofen remained appropriate and that the scheduling of ibuprofen would remain unharmonised at this time, furthermore the Committee asked the Secretariat to draw MEC's attention to the dose limit in the NZ Regulatory Guidelines and recommended that MEC consider including similar requirements in the AGRD vol 2.

DISCUSSION

The Committee noted the response from MEC in June 2003 referring the issue back to NDPSC to clarify the rationale behind the current proposal to restrict the strength of OTC liquid ibuprofen preparations in Australia.

The Committee understood that NZ Medsafe, for practical means, decided to include the strength, pack size and dose requirements for OTC ibuprofen in their Regulatory Guidelines rather than the First Schedule of the Medicines Regulations.

Members noted that current ibuprofen guideline in the AGRD Volume 2 (now called the Australian Regulatory Guidelines for OTC Medicines (ARGOM) lists the dosage recommendations for ibuprofen. However, the ibuprofen ARGOM did not include a section on product strength.

OUTCOME

The Committee agreed that MEC be advised that the NDPSC did not include the strength limits for OTC liquid ibuprofen to allow for Trans-Tasman harmonisation and schedules and that MEC should consider harmonising their guidelines with New Zealand.

13.9 HYOSCYAMUS NIGER

PURPOSE

The Committee considered a cut-off to exempt preparations containing *Hyoscyamus niger* to harmonise with NZ.

BACKGROUND

The 38th (June 2003) NDPSC meeting considered a recommendation of the 28th (November 2002) NZ MCC to amend the cut-off in Appendix G of the SUSDP for atropine (100µg), hyoscine (10µg) and hyoscyamine (10µg) to 300µg/L to harmonise with New Zealand. The Committee agreed to amend the cut-offs in Appendix G for atropine to 300µg, hyoscine to 150µg and hyoscyamine to 100µg to reflect the relative potencies. NZ Medsafe was advised that harmonisation of the scheduling outcome for atropine had been achieved and that Australia would remain unharmonised on the cut-off to exempt hyoscine and hyoscyamine at this time.

The 29th (May 2003) MCC meeting considered a submission from XXXXXXXXXX seeking reclassification of *Hyoscyamus niger* from pharmacy only medicine to general sale medicine when in packs containing 300µg[1] or less of total solanaceous alkaloids. This submission resulted from the recommended cut-offs in Appendix G not allowing general sale status for a *Hyoscyamus niger* product.

The 29th MCC meeting agreed to classify *Hyoscyamus niger* as a general sale medicine when in packs containing 30 micrograms or less of total solanaceous alkaloids. The MCC decision was made on the grounds that the 30µg total solanaceous alkaloid content per pack was within the general principles of the herbal framework adopted in NZ that a general pack should contain not more than one hundredth of the lowest fatal dose.

DISCUSSION

The Committee considered XXXXXXXXXX submission to the NZ MCC and their pre-meeting submission to the NDPSC which proposed that the SUSDP be amended to allow for an exemption for preparations containing 30 micrograms or less of total solanaceous alkaloids per pack to harmonise with NZ.

Members discussed previous harmonisation activities for atropine, hyoscine and hyoscyamine and the XXXXXXXXXX member was concerned that the decision, if agreed, would endorse the general principle of the herbal framework adopted in NZ that a general pack should contain not more than one hundredth of the lowest fatal dose. Members agreed that the decision should be agreed on harmonisation.

A member questioned the relevance of the Appendix G entry for hyoscyamine. It was noted that Appendix G level for hyoscyamine was less than the level for the general sale.

OUTCOME

The Committee agreed to foreshadow, on the grounds of harmonisation, an amendment to the Schedule 2 entry for *Hyoscyamus niger* to exempt preparations containing 30 micrograms or less of total solanaceous alkaloids from the requirements of scheduling.

Foreshadowed for consideration at the February 2004 meeting

[1] The value "300µg" was corrected to read "30µg" at the June 2004 NDPSC Meeting (Item 1.5.2)

Schedule 2 – Amendment

HYOSCYAMUS NIGER – amend entry to read

HYOSCYAMUS NIGER for oral use:

(a) in undivided preparations containing 0.03 per cent or less of total solanaceous alkaloids when labelled with a dose of 0.3 mg or less of total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or

(b) in divided preparations containing 0.03 mg of total solanaceous alkaloids or less per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids,

except in a pack containing 30 micrograms or less of total solanaceous alkaloids.

Schedule 4

HYOSCYAMUS NIGER – amend entry to read

HYOSCYAMUS NIGER **except**:

(a) when included in Schedule 2; or

(b) in a pack containing 30 micrograms or less of total solanaceous alkaloids.

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

14.1 SUSDP, PART 4

14.1.1 ORLISTAT

The Committee considered an application seeking to reschedule orlistat for the treatment of obesity from Schedule 4 to Schedule 3 of the SUSDP.

BACKGROUND

Orlistat is a potent, specific and reversible long-acting gastric and pancreatic lipase inhibitor that limits the breakdown of triglyceride and the absorption of dietary fat. It is used in conjunction with dietary modification in the management of obesity.

XXXXXXXXXX markets XXXXXXXXXX containing 120 mg per capsule of orlistat for the treatment of obese patients with a Body Mass Index (BMI) of ≥30 and overweight patients with a BMI ≥27 in the presence of other risk factors, in conjunction with a mildly hypocaloric diet. Orlistat was first considered by the August 1999 NDPSC meeting and included in Schedule 4 of the SUSDP. The June 2002 NDPSC meeting initially considered a submission from XXXXXXXXXX seeking to reschedule orlistat for the treatment of obesity from S4 to S3, at which the Committee decided that the existing S4 scheduling remained appropriate. The Committee's decision was based on the following:

- The Committee was not satisfied that the safety profile of orlistat was consistent with Schedule 3 medicines, given the wide range of contraindications and potential adverse outcomes associated with obesity.
- The Committee agreed that thorough pre-screening and assessment by medical professional for co-morbidities associated with obesity was essential to determine the patient's suitability for orlistat therapy and reduce the potential for adverse effects.
- The Committee was of the view that making orlistat for the treatment of obesity Schedule 3 medicine would impart the wrong public health message that therapeutic intervention is the first-line treatment for obesity or over-weight conditions, and could expose the public to unnecessary risks. It was stated that consumers should be encouraged to undertake the appropriate lifestyle changes as a first option to achieve safe and long-term weight loss.

A second submission from XXXXXXXXXX to reschedule orlistat for the treatment of obesity from S4 to S3 was submitted to the February 2003 NDPSC meeting, which included a proposal to list orlistat in Appendix H of the SUSDP. However, the Committee agreed that the concerns raised at the June 2002 meeting had essentially remained unresolved and the decision to retain orlistat in Schedule 4 was reconfirmed. The following reasons were provided:

- In the absence of medical assessment of progress and regular monitoring for co-morbidities of patients undergoing pharmacotherapy with orlistat, long-term OTC treatment of this condition was undesirable on public health terms.
- The issue relating to the need for dietary supplementation with fat-soluble vitamins during treatment of orlistat and its overall effect on nutrition remained unresolved.
- Community pharmacists were not equipped to screen for co-morbidities associated with obesity (diabetes etc) and deal with potential adverse effects, and they were not set up to handle the high level of counselling and on-going support required to successfully manage obesity.

The Committee pointed out that any further rescheduling proposal should provide sufficient evidence to support the claim that orlistat is efficacious, safe and appropriate for long term weight loss outside the controlled environment of clinical trials.

DISCUSSION

The Committee noted that XXXXXXXXXX made a new application to reschedule orlistat for the treatment of obesity from S4 to S3. The following points were submitted:

There is no safe and effective over the counter medication available to help the subset of patients who may require pharmacological intervention but do not wish to visit a doctor. On the other hand, consumers have unrestricted access to many unproven OTC medicines for weight loss.

A full study report (XXXXXXXXXX study) of the trial conducted over a 4-year period was submitted to the meeting which confirmed the long term efficacy of orlistat in terms of weight loss and weight maintenance. Also, the study demonstrated that XXXXXXXXXX was more effective than diet and exercise alone and had the effect of delaying the onset of type 2 diabetes and decreasing the hazard of diabetes mellitus by 37.3% compared to placebo. The level of counselling used in the above study was similar to that provided by weight reduction dieticians or in many of the commercial weight reduction programs, i.e. visit once every 2 weeks for the first 25 weeks and then every 4 weeks.

Orlistat has reasonable efficacy in the uncontrolled setting (outside the clinical trial setting) as shown in the findings of the two studies: 1.) An Australian survey of 2131 patients who voluntarily enrolled into the XXXXXXXXXX patient support program (the real world of community use of the product under prescription), and 2.) a post-marketing efficiency study from Germany.

It was claimed that there was no evidence of either vitamin deficiency or bone disease in the 4-year XXXXXXXXXX study.

Pharmacists are well-equipped and trained to provide the required level of counselling and on-going support to consumers, and are well-placed to direct patients to their GP for a health check, where necessary.

- Appendix H brand advertising of XXXXXXXXXX would not again be sought until such time that it was fully supported by the community and pharmacy professional groups.

The Committee noted that the following points were highlighted in the report evaluating the sponsor's rescheduling application:

- The company provided a number of letters of endorsement from leading physicians working the in area of the treatment of obesity. All were in favour of

the rescheduling and their comments were consistent in their appraisal of orlistat and many had addressed the issues raised by the committee.

- There was a wide range of unscheduled products on the market whose efficacy was not evaluated by the TGA and for which many extravagant claims were made. The company in its submission identified a wide range of OTC Listed products including – "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", "XXXXXXXXXX", as well as some food products and weight management programs. Some of the experts have also indicated that a range of very low calorie food products are also available and that these carry some of the same side effects and potential complications as XXXXXXXXXX and are currently available without prescription.
- The product has been shown to be effective and safe in long term studies of up to 4 years. Apart from the 1 and 2 year studies that have been presented previously, the 4-year XXXXXXXXXX study that was briefly presented in the last submission was re-submitted with a summary of the trial and some of the details. The XXXXXXXXXX study compared orlistat added to a moderately hypocaloric diet and moderate increase in exercise to the diet and exercise alone. The results for orlistat were statistically significantly better than placebo at 12 months ($p<0.001$) and at 4 years ($p<0.001$) for percent losing $\geq 5\%$ and $\geq 10\%$. The hazard ratio indicates that orlistat treatment significantly decreased the hazard of diabetes mellitus relative to placebo. The evaluator agrees that the study has given evidence for the long term efficacy, and the effect on development of type 2 diabetes. The counselling visit to a dietician scheduled every 2 weeks for the first 25 weeks and then every 4 weeks for the remainder of the 4 years, which was considered to be similar to that provided by weight reduction dietician or many commercial weight reduction programs.
- The efficacy of the product in the unsupervised setting is difficult to demonstrate but 2 studies are presented which suggest that the efficacy is similar to that which was considered acceptable for nicotine replacement therapy.
- The safety of XXXXXXXXXX appears acceptable for a Schedule 3 product. In response to the Committee's previous concerns over the issues of the fat soluble vitamins and the potential for metabolic bone disease, the company has presented extensive data from the 4-year XXXXXXXXXX study, and demonstrated that neither complications are likely to be a problem with orlistat. Furthermore, data from the company and the experts suggests that the Australian patients are likely to take the drug average for 3 months, which may be partially attributed to the cost XXXXXXXXXX /month). There is potential misuse by inappropriate dietary modification and/or patients eg overweight anorexia nervosa suffers, since the drug does not lead to sudden or excess weight loss. The relationship between GI side effects and fat intake reinforces to the patient the need for fat reduction in the diet.

- The Committee has previously expressed the view that patients should be prescreened for comorbidities before being prescribed the drug. This view was not supported by any of the Experts.

- The data presented addressed the issues raised by the Committee and demonstrated that the product met the criteria for Schedule 3 in terms of safety and efficacy, and for the use intended.

The Committee noted all pre-meeting submissions listed in Attachment 5. The main arguments in support the rescheduling proposal contained in pre-meeting submissions were summarised as follows:

- Obesity is a major public health concern that is currently under-treated. Consumers need greater access to effective weight loss products.
- Orlistat is an effective treatment for obesity, has a favourable safety profile and meets the criteria for inclusion in S3.
- Since obesity is linked to both the onset of pre-diabetes, Type 2 diabetes, and increased complications from Type 2 diabetes. Improvement of individual and community access to orlistat with its support programs will further enhance the outcome of quality education programs for diabetes.
- Its S3 scheduling will provide long term benefits to public health, reduced costs to the health system, and unproved health outlooks and general wellbeing.
- Australian environment is ideal for first OTC experience of orlistat – OTC medicine supply with access to pharmacist assessment and advice in Australia is different from that in the US.
- Pharmacists are well equipped to safely and effectively administer orlistat in the S3 setting and are well placed to provide counselling and advice in many aspects including the combination of lifestyle changes and pharmacological intervention on weight management. In fact, several weight management programs / protocols (Weight Wise Program, Your Weight Your Way, Weight Control Pharmacy Self Care Card) have been developed by the pharmacy profession. The community pharmacy network is well placed to screen for conditions and monitor potential adverse effects, and has the capabilities to assist a customer to identify and select an approach that will be effective for them, and prevent misuse.
- Although treatment with orlistat decreased the mean 25-hydroxy vitamin D, vitamin E and vitamin K1 levels, the mean levels of all vitamins assessed at any time during the 4-year treatment period of the XXXXXXXXXX study remained well within the normal reference ranges. The orlistat Consumer Medicine Information provides an ideal opportunity to discuss the latest evidence regarding the need for fat soluble vitamin supplementation.

The Committee noted the main arguments opposing the rescheduling proposal contained in public submissions:

- More Australian experience should be accumulated with its long-term use before its down scheduling, although orlistat appears to have a fairly benign side effect profile compared with most S4 drugs.
- The preferred first-line treatment for obesity is non-pharmacologic therapies. The S3 scheduling of orlistat may cause wrong public perception for early pharmacotherapy.
- Before a patient embarks on a course of treatment with orlistat, a full medical assessment is necessary, with particular reference to the possibility of diabetes.
- Potential misuse by people with eating disorders, and consequent vitamin deficiencies.
- Unacceptable GI symptoms induced by orlistat combined with a high dietary fat intake.

The Committee noted that orlistat has a relatively good safety profile. In the 1-4 year clinical trials submitted by the sponsor, the product caused a low incidence of severe adverse / side effects which generally required no medical intervention, and with no evidence of significant effects on either vitamin levels or bone disease. It was noted that the sponsor provided a number of letters from physicians who were working in the area of the treatment of obesity who were in favour of the rescheduling.

The Committee accepted the view that most obese patients did not loose body weight through diet and/or exercise alone, and use of orlistat in conjunction with lifestyle changes was more effective and more efficient in patients, including those with non-insulin dependent diabetes mellitus who were under medications. A member questioned orlistat's real efficacy as an OTC product compared to that described in the clinical trials. It was stated that patients generally drop the therapy after 3 to 6 months probably due to unsatisfactory outcome, and high cost. Another member expressed concern regarding the need for treatment related dietary behaviour reinforcement which seemed a key issue for the efficacy of the product. Hence, a reasonable expectation for a gradual and long-term weight loss and the requirement for its use in conjunction with exercise and dietary changes should be indicated in the product information.

Members discussed the potential risk for misuse and overdose of the product. It was noted that increased dose did not increase the efficacy for weight loss, and the product could not be used as an alternative for dietary modification. Furthermore, its relatively low gastrointestinal tolerability was likely to discourage abuse. The likelihood of inappropriate use would be minimised by the requirement for initial counselling by a pharmacist.

The Committee recognised that with good training and extensive experience in weight loss programs, pharmacists were able to appropriately handle patient requirement for S3 availability of this product. Its inclusion in S3 would enhance the accessibility of the product.

Member agreed that a distinction be made between the product for diabetes containing orlistat (XXXXXXXXXX) should remain in S4, and that only orlistat-containing weight loss products (XXXXXXXXXX) for obesity were being considered for rescheduling to S3.

Members noted that the applicant did not apply for inclusion of the product in Appendix H. However, in a disease-awareness advertising campaign, obesity patients were encouraged to talk to their doctors / pharmacists for weight loss. The Committee agreed that since no drug was mentioned in the advertisement, it was not considered to breach the code.

DECISION 2003/39 - 31

The Committee agreed to include orlistat for the treatment of obesity in Schedule 3 of the SUSDP. The decision was made on the following grounds:

- Safety profile of orlistat based on the a low incidence of adverse effects;
- Orlistat was reasonably efficacious for gradual and long term weight loss when used in conjunction with exercise and dietary restriction;
- Obesity is a disease which can be easily recognised by consumers;
- Pharmacists in Australia have good training and experience in providing advice and consultation in relation to management of weight loss and treatment of obesity;
- Orlistat for use in weight loss has low potential for abuse or overdose.

Schedule 3 - New entry

ORLISTAT in oral preparations for weight-control purposes containing 120 mg or less of orlistat.

Schedule 4 - Amendment

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

14.1.2 PARACETAMOL / CAFFEINE

PURPOSE

The Committee considered an application seeking to include paracetamol 500 mg when combined with caffeine XXXXXXXXXX in a tablet when in a 50 tablet pack in Schedule 2.

BACKGROUND

Paracetamol is a p-aminophenol derivative that inhibits analgesic and antipyretic effects without anti-inflammatory activity. Paracetamol is currently in Schedule 4 when combined with aspirin, caffeine, or salicylamide or any derivative of these substances. It is in S2 for all other therapeutic uses except when in small packs which are unscheduled. Caffeine is currently an unscheduled substance, which is allowed to be included in a number of foods and beverages at concentrations of up to 320 mg/L in formulated caffeine beverages.

In the 1960s – 70s in Australia, analgesic combinations containing aspirin, phenacetin (paracetamol from 1975) and caffeine, or aspirin, salicylamide and caffeine were found to be associated with a high risk of analgesic abuse and consequent analgesic nephropathy. Combinations of any two or more or paracetamol, aspirin, salicylamide, caffeine or any derivatives of these substances were rescheduled from over the counter products to prescription-only products following a recommendation from XXXXXXXXXX in 1977.

XXXXXXXXXX sought an amendment to the SUSDP to include in Schedule 2, XXXXXXXXXX which contain a fixed dose of paracetamol 500 mg and caffeine XXXXXXXXXX. The product is in a pack containing 50 tablets (25 grams paracetamol and XXXXXXXXXX caffeine). The proposed indication was “for the temporary relief of self-limiting pain conditions and the reduction of fever”.

DISCUSSION

The Committee noted the following main points had arisen in the application and a pre-meeting submission by the applicant:

- The combination of paracetamol and caffeine is currently available OTC in small pack sizes in a number of other markets for various periods, including the UK (15 years), New Zealand (3 years), and has an excellent safety profile.
- The rationale for combining paracetamol with caffeine is that it provides superior analgesia with a faster onset of action compared to paracetamol alone. There is substantial evidence that caffeine potentates the action of minor analgesics.
- The amount of caffeine present in a single dose (two tablets) is XXXXXXXXXX, which is similar to that in a medium strength cup of coffee (100mg).
- The association between combination analgesic abuse and analgesic-associated nephropathy (AAN) shown in the data review from 1962 to 1972, was related to the triple combination products (aspirin, phenacetin and caffeine [XXXXXXXXXX], or aspirin, salicylamide and caffeine [XXXXXXXXXX]. However, a prospective review (Kidney International 2000) in renal medicine concluded that sufficient evidence is absent to associate non-phenacetin combined analgesics (paracetamol and caffeine) with nephropathy, and that new studies should be done to provide appropriate data for resolving this question.
- Currently there are no combined caffeine analgesic products on the Australian market, although products containing a single ingredient, paracetamol 500mg (XXXXXXXXXX and others) or caffeine 100mg (XXXXXXXXXX), are available and exempt from scheduling.
- There is a need for access to a product that produces faster, more effective pain relief than paracetamol alone. Schedule 2 access to the combination product would provide pharmacists with a new option with which to aid patients with acute pain, particularly headache and migraine. This would be particularly important for those patients for whom non-steroidal anti-inflammatory agents are contraindicated.

The Committee noted that the evaluation report stated the following:

- The co-administration of caffeine with paracetamol increases both the rate of onset and the size of the analgesic effect, although the mechanism of this effect remains unknown. A meta-analysis (Laska et al 1984) indicated that paracetamol alone would have to be given in a 37% higher dose to achieve the same effect as the combination, and the onset of action was also significantly more rapid. Further clinical trials in tension headache have demonstrated a statistically significant superiority of paracetamol 1000 mg with caffeine 130 mg (2 tablets in a single dose) over paracetamol alone (Migliardi et al 1994).

There is also evidence from animal experiments that caffeine has direct antinociceptive effects (Sawynok and Yaksh 1993).

- Despite extensive epidemiological and experimental investigation, there is no evidence that a paracetamol-caffeine combination is associated with analgesic-associated nephropathy (AAN). A descriptive review (Whelton 1999) of drug-induced renal toxicity states that caffeine is not an independent nephrotoxin. In addition, there is little evidence, either experimental or epidemiological, that paracetamol alone is capable of inducing analgesic nephropathy (Blantz 1996). A position statement from the National Kidney Foundation (USA, 1996) states that there is experimental evidence indicating that very large doses of paracetamol (0.5-1.0 g/kg for weeks to months) can cause renal papillary necrosis, but that there is only a weak association between habitual use of paracetamol and end-stage renal failure. Although this paper recommends against the use of compound analgesic preparations (eg. aspirin + paracetamol), insufficient data were available on the effects of paracetamol + caffeine to make a recommendation in relation to this combination. More recent reviews of the literature on analgesic-caffeine combinations (Bach et al 1998; Feinstein et al 2000) conclude that there is no compelling evidence to support the argument that caffeine induces craving for, or misuse of, analgesic formulations in the majority of users.

- Caffeine is a widely available unscheduled substance with a well-understood toxicological profile and a wide therapeutic index. Paracetamol has a moderately narrow therapeutic index, is well tolerated when used therapeutically, but has significant hepatotoxicity when taken in overdose (usually intentional). The potential toxicity of the combination from overdose is similar to that of paracetamol alone, which can cause serious hepatotoxicity at relatively small overdoses (12 g in 24 tablets or more), and 50 tablets has the potential to cause lethal hepatotoxicity if consumed as a single dose. The total dose of caffeine present in a full pack of 50 tablets could also cause serious toxicity if ingested as an overdose, but has a low risk of lethality. However, since overdosage of caffeine is likely to produce nausea and vomiting, this could help to protect a patient from fully absorbing the paracetamol.

- A risk-benefit comparison of the proposed combination product with paracetamol alone suggests that the combination has similar risks and increased benefit.

- There is sufficient safety information in relation to this specific combination of paracetamol and caffeine, to overturn the 1977 XXXXXXXXXX recommendation that any analgesic combination including caffeine should be included in Schedule 4 due to potential analgesic nephropathy.

The Committee noted the pre-meeting submission received from XXXXXXXXXX who did not support the proposal of S2 scheduling. XXXXXXXXXX expressed concerns on: (1) the uncertainty of caffeine enhancing the analgesic action of paracetamol; (2) the experience of the high incidence of analgesic nephropathy in Australia in the 1970s; (3) the addition of a sought-after stimulant may encourage the excessive or improper consumption of paracetamol. Hence, there seemed little justification for amending the schedule entries.

Members questioned the rationale for the combination of paracetamol with caffeine, although the sponsor claimed that caffeine potentiated the action of paracetamol by increasing both the rate of onset and the size of the analgesic effect. A member pointed out that a dose of caffeine > 250 mg/day might cause cardiovascular effect, whereas the total amount of caffeine in a daily dose of 8 tablets was XXXXXXXXXX. Members further discussed whether it was necessary to add caffeine to paracetamol for reducing headache, how robust the data were from the study (Laska et al 1984) which showed enhancement of the analgesic effect of paracetamol, and whether paracetamol in this tablet (500 mg) was enough for reducing fever.

Members extensively discussed the public health benefit and potential risk for down-scheduling of the combined analgesic preparations with caffeine. Caffeine was a substance to which people had daily broad/extensive exposure. Some degree of dependency/addiction to caffeine, probably rebound headache following withdrawal, might lead to excess use, or abuse of the caffeine-containing product. This mechanism might be related to enhanced utilisation of combination analgesics and analgesic-associated nephropathy in the past. Since the original S4 setting for the combination of analgesic and caffeine was based on the concern on analgesic nephropathy in Australia, epidemiological evidence for negative renal problems was not solid enough to allow for down-scheduling. Hence, the benefit gained by adding caffeine into paracetamol, if any, was offset by its risk.

Members were informed that it was recommended by TGA that all complementary medicine products containing caffeine should be indicated in the label. This product should also be labelled similarly if the down-scheduling was to proceed.

OUTCOME

The Committee agreed that the current scheduling of paracetamol and caffeine remains appropriate. XXXXXXXXXX containing a fixed dose of paracetamol 500 mg and caffeine XXXXXXXXXX "for the temporary relief of self-limiting pain condition and the reduction of fever" was not included in Schedule 2 of the SUSDP for the following reasons:

- There was inadequate evidence provided to demonstrate that the combination of caffeine and paracetamol was safe.

- Caffeine had potential toxic/side effects at high doses, but no convincing therapeutic benefit.
- The stimulating nature of caffeine might encourage excessive use or abuse of the product.

14.1.3 FLUTICASONE

PURPOSE

The Committee considered rescheduling fluticasone propionate for the short-term (3-6 months) prophylaxis or treatment of allergic rhinitis in adults and children aged 12 years and over.

BACKGROUND

Fluticasone propionate is a semi-synthetic trifluorinated glucocorticoid that has local anti-inflammatory activity and a potency of about twice that of beclomethasone dipropionate.

XXXXXXXXXX (fluticasone propionate) was approved for registration in Australia on 13th January 2000, as a Schedule 4 product. It was rescheduled to S3 status in November of 2000 for short-term prophylaxis or treatment of seasonal allergic rhinitis and launched as a non-prescription product in July 2001 (under the brand name XXXXXXXXXX). The S3 indications were amended in November 2001 to include perennial allergic rhinitis.

XXXXXXXXXX submitted an application to reschedule intranasal fluticasone propionate from Schedule 3 to Schedule 2 for the prophylaxis and treatment of allergic rhinitis, including hayfever, in adults and children aged 12 years and over, when supplied in packs containing 120 doses or less.

DISCUSSION

The Committee noted the following points highlighted in the application:

- Intranasal corticosteroid sprays, such as fluticasone, have high efficacy, and are more effective in control symptoms of allergic rhinitis than do antihistamine tablets which are S2 products and indicated for the treatment of this disease, and are considered to be first line therapy by many specialists in the allergy field.
- The good safety profile of intranasal fluticasone propionate with minimal risk of systemic side effects is demonstrated by extensive worldwide and local experience in the treatment of allergic rhinitis.
- Fluticasone propionate has a comparable safety and efficacy profile to the other intranasal corticosteroids, beclomethasone, budesonide and mometasone which have been rescheduled to S2.

- The product has similar properties to other topically active steroids, but has extremely low oral bioavailability (<1.0%) than others, and thus an improved therapeutic index (ratio).
- Hayfever and many perennial allergies are easily self-diagnosed by their characteristic nasal symptoms and its seasonal nature.
- Fluticasone has been available as a non-prescription medicine in Australia for 2-years and almost 4 years in New Zealand. Post marketing surveillance confirms that the product did not pose safety concerns more than other corticosteroids sold as S2 products.

The Committee noted the main points summarised in the evaluation report on the submission:

- Due to its very low bioavailability, there is little evidence of significant systemic adverse events with fluticasone intranasally, in particular no suppression of hypothalamic-pituitary axis function following dosing up to 800 μg/day for 4 weeks. There have been no cases of abuse or overdose.
- Periodic Safety Update Report (PSUR), data received and updated by XXXXXXXXXX of XXXXXXXXXX, indicates that there were XXXXXXXXXX patient-years of exposure to intranasal fluticasone propionate from 1 September 2002 to 31 December 2002. In addition to respiratory (epistaxis and nasal septal perforation) and eye disorders (cataract and glaucoma), there was one case of acute adrenal crisis following receiving an unspecified dose of intranasal fluticasone, and budesonide concomitantly. Generally, there appeared to be no worrisome or otherwise previously unrecognised adverse events or increase in frequency of the expected adverse event profile.
- The product fulfils the relevant criteria for S2 listing, including its safe by in use with a wide therapeutic index and a low incidence of adverse effects; available pharmacist advice or counselling if necessary; easily recognised indications (minor ailments or symptoms) by consumer; low potential for abuse or inappropriate use; and low likelihood of masking serious disease.

Members noted the pre-meeting comment from XXXXXXXXXX opposing the rescheduling of intranasal fluticasone to S2, and raising the concerns on the potency of this steroid, a potential risk of overdose or cumulative exposure, and consequent adverse effects.

Members considered the extremely low bioavailability (< 1%) of fluticasone, and the aqueous nasal spray for short-term use (3-6 months) in prophylaxis or allergic rhinitis showing low potential for adverse effects (sneeze, running nose), rare cases in suppression of hypothalamic-pituitary axis function, and its low potential for overdose or abuse. The Committee agreed to reschedule intranasal fluticasone propionate from Schedule 3 to Schedule 2, and removal from Appendix H.

DECISION 2003/39 - 32

The Committee agreed to include intranasal fluticasone propionate in Schedule 2 for the prophylaxis and treatment of allergic rhinitis in adults and children aged 12 years and over, when supplied in packs containing 120 doses or less, and removal from Appendix H. The decision was based on:

- Its safety in use with a wide therapeutic index and a low incidence of adverse effects;
- Available pharmacist advice or counselling if necessary;
- Use for minor ailments or symptoms which can be easily recognised by the consumer;
- Its low potential for abuse or inappropriate use; and
- Its low likelihood of masking serious disease.

Schedule 2 – New Entry

FLUTICASONE in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in 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

FLUTICASONE - delete entry.

Schedule 4 – Amendment

FLUTICASONE – amend entry to read:

FLUTICASONE **except** when included in Schedule 2.

Appendix H – Amendment

Fluticasone – delete entry.

14.1.4 KAVA (*PIPER METHYSTICUM*)

PURPOSE

The Committee considered scheduling of kava (*Piper methysticum*) which contains kavalactones as the active constituents.

BACKGROUND

Piper methysticum (kava) is a member of the pepper family (Piperaceae), and has a wide distribution throughout the Pacific. Kava has been used in traditional medicine to treat venereal disease, gout, rheumatism, diarrhoea, asthma, and to calm nervous children and induce women's breast milk flow. Pharmacologically, kava is described as having an anxiolytic effect, is a muscle relaxant and has anticonvulsant and spasmolytic activity. It is a sedative and can depress the limbic system. Its effects appear to be mainly due to the activity of the compounds in the lipid soluble resin – the kavalactones. The pharmacological properties of kava are comparable to those of benzodiazepines, although kavalactones bind very weakly to GABA-A and benzodiazepine receptors. More recently, kavalactones have been extracted for therapeutic products by volatile solvent extraction.

During 1988 to 1990, the Committee considered scheduling of kava and agreed to include kava in Schedule 4 in order to prevent its widespread consumption in XXXXXXXXXX. The S4 entry was deleted by the August 1992 Meeting, due to the introduction of a Kava Control Act in XXXXXXXXXX, and there being no need to schedule kava in other States. During 1997 and 1998, the re-scheduling of kava was returned to the Committee for consideration since therapeutic preparations containing kava were marketed in Australia and had been included as listable products on the Australian Register of Therapeutic Goods (ARTG). However, the Complementary Medicines Evaluation Committee (CMEC) advised that therapeutic products containing kava could be controlled adequately through the listing and registration systems, rather than by poison scheduling. The recommendation was that kava would be a listable substance in products containing up to 125 mg of kavalactones per dose, with a recommended daily dose of no more than 250 mg, or a maximum amount of dried rhizome per tea bag of 3 g. Products containing in excess of these amounts would be required to go through the registration rather than the listing process, and would require evidence of efficacy as well as safety. Hence, a foreshadowed S4 decision was not progressed by the Committee at the May 1998 NDPSC Meeting.

Concerns were raised internationally in 2001 over liver toxicity associated with kava-containing medicines, which was involved in 82 adverse reaction reports including 4 deaths. In July 2002, the Adverse Drug Reactions Advisory Committee (ADRAC) received a report of the death, from complications of liver failure, of a woman in Australia who had been taking a kava-containing medicine for four months. As a consequence, the TGA, acting on the advice of CMEC and ADRAC, instigated a voluntary recall of medicines containing kava. Kava has also been authorised/voluntarily withdrawn from the market in Canada, UK, Germany and Singapore.

The TGA invited industry to provide evidence that kava is safe for human consumption before making a final decision on any change to the regulatory status of kava. During 2003 the OCM completed a safety evaluation of kava containing medicines, which was reviewed by XXXXXXXXXX. XXXXXXXXXX was requested to review the safety of kava (*Piper methysticum*) and to make a recommendation to CMEC on whether or not kava is suitable for use as an ingredient in listed medicines.

DISCUSSION

The Committee noted the evaluation report provided by XXXXXXXXXX to the CMEC which highlighted the following points:

Toxicology studies on kava have been limited mainly to acute and subchronic studies in mice and rats. The LD50 was estimated between 800 to 1000 mg/kg for the oral intake of the different kavalactones investigated. While the dosage in the therapeutic industry is typically up to 250 mg/day of kavalactones (4.2 mg/kg/day for a person with body weight of 60 kg), and it can vary considerably (up to 3800 mg/hour) when kava is consumed as a drink.

Absorption of kavalactones via the gastrointestine is poor and variable. Kavalactones appear to be hydroxylated by the cytochrome P-450 system (CYP enzymes) and are eliminated by the kidneys and in the faeces. CYP enzyme deficiency may possibly be a risk factor with respect to kava hepatotoxicity. There is the possibility that genetic polymorphism of the CYP enzymes may underlie the potential for kava hepatotoxicity even at low dose rates. Increased liver enzymes (GGT, ALT, AST and/or ALP) were observed in some human cases. Kava might: (a) have additive effects with benzodiazepines, (b) antagonise central dopaminergic mechanisms and (c) intensify the effects of alcohol.

Internationally, there have been 82 reports of liver toxicity associated with the use of kava-containing medicines including 4 deaths. The severity of the liver damage varies from abnormal liver function tests to liver transplantation. The TGA review of these case reports indicates that there are a number of the cases where the association of the kava-containing medicine with the adverse event has been rated as possible. However, there do not appear to be any trends between either the adverse event or the severity of the adverse event and age/sex of the patient, product, dose or product form. On 30 July 2002, the ADRAC received a report of the death, from complications of liver failure, of a woman in Australia who had been taking, among other medicines, a kava-containing medicine for four months. The use of a kava-containing medicine was the only factor in the woman's medical history that could be identified as a possible cause of her liver failure.

XXXXXXXXXX recommended options to CMEC for regulation of kava which were:

> (1). The TGA does not allow *Piper methysticum* to remain an ingredient in listed medicines; or
>
> (2). The TGA allows *Piper methysticum* to remain an ingredient in listed medicines, with label warnings or advisory statements, restriction to practitioner dispensing only, restriction to certain extraction methods, restriction to certain plant parts, and/or only allow kava in the form of the throat sprays or topical formulations.

Additionally XXXXXXXXXX also suggested that the scheduling of *Piper methysticum* may also be an option. It was pointed out that scheduling would result in the removal of kava as a listable ingredient, and thus kava-containing products would have to be registered.

The Committee noted that the 41st Meeting of CMEC considered XXXXXXXXXX recommendations concerning the suitability of kava for use as an ingredient in listable medicines. The CMEC made a number of recommendations including Recommendation 41.3. The Committee agreed with the CMEC Recommendation 41.3 that products containing *Piper methysticum* must be Registered prior to their supply, other than:

(i) Aqueous dispersions of whole or peeled rhizome of *Piper methysticum*;
(ii) Aqueous extracts of whole or peeled rhizome of *Piper methysticum*;
(iii) Dried whole or peeled rhizome of *Piper methysticum*;
(iv) Products for topical application to the skin; and
(v) Homoeopathic preparations more dilute than a thousand fold dilution of a mother tincture;

which may be included in Listed medicines under certain conditions.

Aqueous dispersions and extracts of whole or peeled rhizome of *Piper methysticum*as as well as dried whole or peeled rhizome of *Piper methysticum*as were considered by CMEC to be suitable for use as ingredients in Listed medicines for oral use, subject to the following conditions:

(a) the preparation does not contain, for its recommended daily dose, more than 250 mg of kavalactones; and
(b) if the preparation is in a tablet or capsule – the amount of kavalactones does not exceed 125 mg for each tablet or capsule; and
(c) if the preparation is in a tea bag – the amount of dried whole or peeled rhizome does not exceed 3 g for each tea bag; and
(d) if the preparation contains more that 25 mg of kavalactones per dose – the label on the goods includes the following warnings (or words to the same effect):
    - Not for prolonged use. If symptoms persist, seek advice from a healthcare practitioner.
    - Not recommended for use by pregnant or lactating women; and
    - May harm the liver.

Such preparations were also considered by CMEC to be suitable for use as ingredients in Listed medicines for the topical application to the rectum, vagina and by spray to the throat.

CMEC further recommended that *Piper methysticum*as may be used as an ingredient in Listed medicines for topical applications to the skin.

Additionally, it was pointed out that the NDPSC was requested by the Non Prescriptions Medicine Branch to:

- note the recommendations of the CMEC;
- consider the need for possible restrictions on the supply of kava containing products containing other than what is stipulated in the CMEC Recommendations, which are extemporaneously compounded and dispensed by health care practitioners;
- consider the need for possible restrictions on the regulation of alcoholic extracts of kava that are supplied to health care practitioners in bulk as starting materials for extemporaneously compounding; and
- note that TGA does not regulate sole traders in States and Territories, raw material suppliers and personal importers. Therefore, there remains the potential for supply of non-aqueous extracts of kava.

The Committee noted an article entitled "Sit-down drink"published in Sydney Morning Herald on 16 September 2003. It was reported in the article that a researcher at the Menzies School of Health Research believes that kava is a strong muscle relaxant and may disturb normal heart function, a factor that may exacerbate a pre-existing heart disease. It was also reported that this researcher had found no indicators of long-term liver damage in kava users in Arnhem Land. He did, however, find reversible changes in liver function.

Members were aware of that kava has a long history of traditional use as a beverage or medicine. In recent years, solvent extraction methods have been employed, either an ethanol:water or acetone:water mixture to produce therapeutic products containing a total kavalactone content of 30% to 70%, respectively. There were 84 products on the ARTG which contain *Piper methysticum*, the majority was extracts (95%) and the rest was dry herb.

The Committee noted that prior to the voluntary withdrawal of kava-containing medicines in Australia, the maximum recommended daily dose permitted for Listed medicines was 250 mg of kavalactones with a maximum amount per tablet or capsule of 125 mg and a maximum amount of dried rhizome per tea bag of 3 g. In a clinical trial under recommended therapeutic doses (mostly 60 – 240 mg/day kavalactones for 1-4 weeks), a good efficacy in reduction of anxiety was achieved, while little / mild adverse effects (stomach complaints, restlessness, tiredness, drowsiness), rather than liver toxicity, were involved.

Members further noted that elevated liver enzymes (GGT, ALP-alkaline phosphatase, but a normal ALT level) were associated with heavy drinkers/users of kava. The toxicity might be related to some mechanisms including induction of liver enzymes, an immunoallergic mechanism, or a genetic polymorphism of the CYP enzymes. In the review of case reports, severe liver toxicity which led to liver transplant or death, occurred in individuals taking extracts of alcohol or acetone, and mostly in females. There appeared no dose-response relationship in the toxicity. Members noted that the

method of extraction played an important role in toxicity. The hepatotoxicity of extracts varies significantly, with water extract being the least hepatotoxic and the organic solvents (ethanol, acetone and hexane) being the most hepatotoxic.

Members were informed that kava came to XXXXXXXXXX in XXXXXXXXXX about 20 years ago as a peaceful alternative to alcohol, and became popular with Aboriginal communities. In 1998, XXXXXXXXXX government banned kava. The XXXXXXXXXX member mentioned that XXXXXXXXXX now controlled kava through the Kava Management Act (administered by XXXXXXXXXX). From last year, the XXXXXXXXXX Government allowed restricted supply under licence to some communities, and one person could buy 800 g a week. It was also pointed out by the XXXXXXXXXX member that kava had been restricted in XXXXXXXXXX for several years, and was only allowed to be used with a special licence, for ceremonial purposes or for clinical trials. No listed medicines containing kava were allowed in XXXXXXXXXX.

Members were informed that New Zealand currently did not restrict kava, and it was sold as food, drink or dietary supplements which was equivalent to listable products in Australia. The Committee was advised that XXXXXXXXXX was currently undertaking a review of kava in food, and urged the Secretariat to seek advice from XXXXXXXXXX regarding the outcome of the review.

Members noted the current international regulatory status of kava products. Restrictive regulatory action on voluntary withdrawals from the market have occurred in Canada, UK, Germany and Singapore. The USA and South Africa have issued consumer and professional advisory notices regarding the safety of kava.

OUTCOME

The Committee considered the need for possible restrictions on the regulation of alcohol/acetone extracts of kava that were supplied to health care practitioners in bulk as starting materials for extemporaneously compounding.

The Committee agreed that there was a risk of liver toxicity with use of non-aqueous extracts of kava plants at high doses, and that a schedule entry to minimise this risk without affecting the current usage of listed complementary products should be made following the review of the listed products on the ARTG.

14.2 SUSDP, PART 5

14.2.1 APPENDIX F – CONSIDERATION OF WARNING STATEMENTS FOR S2 PRODUCTS

PURPOSE

The Committee considered a proposal to amend Appendix F, Part 3 entries for acetic acid, chloroform, ether, sodium fluoride and carbon tetrachloride to include Schedule 2 substances.

BACKGROUND

An editorial review of Appendix F, Part 3 highlighted a number of entries that required amendments to include Schedule 2 substances.

DISCUSSION

The Committee thought it appropriate to defer consideration on this item until a list of all affected products could be determined.

OUTCOME

The Committee agreed to defer this agenda item to the February 2004 meeting to allow time for the Secretariat to prepare a list of all products that would be affected by the proposed amendments. The Committee also agreed to foreshadow the proposed amendments.

14.2.2 APPENDIX G

14.2.2.1 MERCURY

PURPOSE

The Committee considered the scheduling of mercury.

BACKGROUND

A request was received to clarify whether 10 ppm of mercury for human therapeutic use is exempt from scheduling under the general exemption in Part 1 – Interpretation of the SUSDP.

The tolerable limit for total mercury, set at the 16th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and maintained after reconsideration at the 22nd JETCFA meeting, was 0.3 mg per person per week, equivalent to 5 µg/kg bw/week. This limit has also been adopted by Food Standards Australia and New Zealand.

DISCUSSION

The Committee was informed that the general exemption in Part 1 – Interpretation of the SUSDP for substances at concentrations of less than or equal to 10 mg/kg or 10 mg/L did not apply to mercury. This was because mercury was also included in Schedule 7.

Furthermore, it was highlighted that mercury was not currently listed in Appendix G suggesting that a safe limit for the use of mercury in dilute preparations for therapeutic use had yet to be determined.

Based on the weekly tolerable limit for mercury through the food pathway, it was proposed that an entry for mercury be included in Appendix G of the SUSDP at a level of 5 μg.

OUTCOME

In the absence of better evidence regarding a safe limit for the use of mercury in dilute preparations, the Committee agreed to foreshadow the inclusion of mercury in Appendix G at the level of 5 micrograms.

Foreshadowed for consideration at the February 2004 meeting

Appendix G – new entry

MERCURY	5 micrograms

15. MATTERS REFERRED BY THE AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC)

15.1 NEW SUBSTANCES

15.1.1 PIMECROLIMUS

PURPOSE

The Committee considered the scheduling of pimecrolimus, a new medicine.

BACKGROUND

Pimecrolimus is an ascomycin macrolactam derivative related to tacrolimus and sirolimus and acts by inhibiting the transcription of early cytokines and pro-inflammatory mediators from T cells and mast cells.

DISCUSSION

The Committee noted the April 2003 ADEC minutes.

The Drugdex monograph on pimecrolimus reported that topical pimecrolimus was indicated for the treatment of atopic dermatitis in adults and children over 2 years of age. Additionally, a section in the Patient Instructions for XXXXXXXXXX included a warning that the medicine should not be used on children under 2 years of age.

The Committee agreed that a restriction regarding the use of pimecrolimus on infants under 2 years of age was required at this stage. However, in view of the issues raised at the April 2003 ADEC meeting, the NDPSC Member asked that ADEC clarify its recommended indication for use on infants 3-23 months of age.

The Committee noted that pimecrolimus was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 33

The Committee agreed to include pimecrolimus in Schedule 4 of the SUSDP on the grounds that the safe use of this medicine required ongoing patient management and monitoring by a medical professional.

Schedule 4 - New entry

PIMECROLIMUS.

15.1.2 ARIPIPRAZOLE

PURPOSE

The Committee considered the scheduling of aripiprazole, a new medicine.

BACKGROUND

Aripiprazole is an atypical antipsychotic agent indicated for the treatment of schizophrenia.

DISCUSSION

The Committee noted the April 2003 ADEC minutes and the approved Product Information for XXXXXXXXXX.

The Committee also noted that aripiprazole was not a classified medicine in New Zealand.

DECISION 2003/39 - 34

The Committee agreed to include aripiprazole in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

ARIPIPRAZOLE.

15.1.3 ANAKINRA

PURPOSE

The Committee considered the scheduling of anakinra, a new medicine.

BACKGROUND

Anakinra is a recombinantly XXXXXXXXXX which antagonises the effect of the IL-1 cytokine in inflammatory joint disease. The recommended dose is Xmg/kg once daily by XXXXXXXXXX XXXXXXXXXX.

DISCUSSION

The Committee noted the April 2003 ADEC minutes and the approved Product Information for XXXXXXXXXX.

The Committee also noted that anakinra was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 35

The Committee agreed to include anakinra in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

ANAKINRA.

15.1.4 EZETIMIBE

PURPOSE

The Committee considered the scheduling of ezetimibe, a new medicine.

BACKGROUND

Ezetimibe is a new chemical entity representing a new class of agents for the treatment of hypercholesterolaemia. Ezetimibe acts to reduce absorption of dietary cholesterol from the intestine. However, the pharmacological mechanism and site of action of the drug has not been elucidated and therefore it is not clear whether the drug works at the site of the brush border, although it is thought to act locally in the intestines.

DISCUSSION

The NDPSC noted the minutes of the April and June 2003 ADEC meetings and the approved Product Information for XXXXXXXXXX.

The NDPSC also noted that ezetimibe was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 36

The NDPSC agreed to include ezetimibe in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

EZETIMIBE.

15.1.5 GEFITINIB

PURPOSE

The Committee considered the scheduling of gefitinib, a new medicine.

BACKGROUND

Gefitinib acts via receptor tyrosine kinase inhibition. Gefitinib inhibits the effects of epidermal growth factor. [Sentence deleted]. Gefitinib inhibits this part of the receptor and as a result inhibits the transmission of intracellular signals responsible for cell survival and proliferation. Several solid tumours, including non small cell lung cancer, are known to over-express EGFR.

DISCUSSION

The Committee noted the Drugdex monograph on gefitinib, which reported that the FDA had classified gefitinib as Pregnancy Category D (studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the foetus. However, the benefits of therapy may outweigh the potential risk). The Committee agreed that inclusion of gefitinib in Appendix D was not warranted as it has a standing policy of not including anti-cancer agents in Appendix D of the SUSDP on the basis of their mode of action.

The Committee noted that gefitinib was classified as a prescription medicine in New Zealand.

DECISION 2003/39 - 37

The Committee agreed to include gefitinib in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

GEFITINIB.

15.1.6 FENOFIBRATE

PURPOSE

The Committee considered the scheduling of fenofibrate, a new medicine.

BACKGROUND

Fenofibrate is an analogue of XXXXXXXXXX and is used in the treatment of hyperlipoproteinemias.

DISCUSSION

The Committee noted the minutes of the April 2003 ADEC meeting.

The Committee also noted that fenofibrate was not a classified medicine in New Zealand.

DECISION 2003/39 - 38

The Committee agreed to include fenofibrate in Schedule 4 of the SUSDP on the grounds that the condition bring treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Schedule 4 - New entry

FENOFIBRATE.

15.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

15.3 OTHER ADEC MATTERS FOR CONSIDERATION

15.3.1 PANCREATIC ENZYME EXTRACT

PURPOSE

The Committee considered scheduling of pancreatic enzyme extract.

BACKGROUND

Pancreatic enzyme extract products are marketed in Australia to treat pancreatic insufficiency and non-specific gastrointestinal conditions. Products containing more than 20,000 BP units of lipase are classified as prescription medicines, while those containing 20,000 BP units or less of lipase can be supplied without prescription. These products include lipase, amylase and protease in varying concentrations, and are used to treat pancreatic exocrine insufficiency including cystic fibrosis, chronic pancreatitis, post pancreatectomy, gastrointestinal by-pass surgery and ductal obstruction. Other non-prescription pancreatic enzyme products, often combined with other complementary medicines, are indicated for use to prevent dyspepsia, to assist digestion, and to prevent flatulence.

In June 2002, the French Health Product Safety Agency (FHPSA) initiated action to limit the marketing of pancreatic enzyme extracts in France to the treatment of exocrine pancreatic failure, due to the potential for porcine parvovirus (PPV) contamination of the products. The FHPSA decided that while the risk/benefit balance justified the continued marketing of such products for serious medical conditions associated with exocrine pancreatic failure, the risk/benefit balance did not justify the continued marketing of the products for less serious conditions. Since 1995, the US FDA has required sponsors of products "labelled, represented or promoted for OTC use in the treatment of exocrine insufficiency" to undergo the same evaluation as prescription drugs, while there are also relevant products marketed as "nutritional supplements". In the UK, it appears that porcine pancreatic enzyme products are approved only for use in pancreatic insufficiency.

DISCUSSION

The Committee noted that the following points were highlighted in XXXXXXXXXX and relevant information provided:

Contamination of Australian marketed pancreatic enzyme products with PPV cannot be ruled out based on the data supplied by the Sponsors.

There is no evidence that the presence of PPV in oral pancreatic extracts intended for human use results in human infection. Although there is a theoretical risk that the PPV could be transmitted to humans, there is no evidence that this would result in disease. However, it is possible that PPV might be a marker for other porcine viruses in pancreatic extracts with the potential to infect humans and cause disease.

The available data suggest that the benefits associated with treatment of pancreatic exocrine insufficiency with porcine pancreatic enzymes outweigh the potential risk of PPV contamination of these products.

The risk-benefit ratio for the use of porcine pancreatic enzymes for conditions unrelated to pancreatic insufficiency (eg. dyspepsia), or as complementary medicines is too high,

and consideration will need to be given to cancelling their listing. In fact, in the absence of any proven benefits, there is a potential risk, however small.

The Product Information (PI) and Consumer Medicine Information (CMI) documents for all porcine pancreatic enzyme extract products should contain relevant information on PPV. Sponsors should be advised to vigorously pursue satisfactory viral inactivation methods.

The XXXXXXXXXX recommended that the use of these products should be restricted to indications for conditions characterised by pancreatic exocrine enzyme insufficiency. The risk-benefit ratio was unfavourable for the use of these products for complementary medicine indications. Hence, those products indicated for conditions other than pancreatic exocrine enzyme insufficiency should be withdrawn.

Members noted that XXXXXXXXXX investigated the potential PPV contamination of porcine pancreatic enzyme products, and recommended necessary regulations based on risk-benefit analysis. The Committee agreed with XXXXXXXXXX recommendations: 1). the benefits associated with treatment of pancreatic exocrine insufficiency (including cystic fibrosis, chronic pancreatitis, post pancreatectomy, gastrointestinal by pass surgery and ductal obstruction) with porcine pancreatic enzymes outweighs the potential risk of PPV contamination, and these products should be included in Schedule 4 and supplied on prescription only. 2). the risk-benefit ratio was unfavourable for the use of porcine pancreatic enzyme-containing products for complementary medicine indications, and hence should be withdrawn.

The Committee noted that on the current Australian market, pancreatic extracts used as essential medication for patients with pancreatic exocrine insufficiency included those containing > 20,000 BP units of lipase (XXXXXXXXXX and XXXXXXXXXX) for supplying on prescription only, and others containing ≤ 20,000 BP units of lipase (XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX) for supplying without prescription. Members were informed that these non-prescription products with lower lipase (≤ 20,000 BPU) were mainly used in patients with cystic fibrosis (CF) to avoid unwanted secondary effects induced by overdose. Hence, the CF patients would be affected and disadvantaged by the inclusion of these products in S4. The Committee asked the XXXXXXXXXX representative to advise XXXXXXXXXX of the foreshadowed consideration on this issue in the February 2004 Meeting.

The Committee also noted that the S4 inclusion would affect some complementary medicine products containing pancreatic enzyme which were indicated for use to prevent dyspepsia, to assist digestion, and to prevent flatulence. The Secretariat was requested to inform the XXXXXXXXXX of the foreshadowed consideration of regulatory actions proposed by XXXXXXXXXX at the next NDPSC meeting, and to seek relevant comments.

A member informed that in addition to complementary medicine products, there were also some OTC products containing pancreatic enzyme which would be affected by S4

inclusion. The Committee agreed that gazetting the item for consideration in the February 2004 Meeting would allow for public comments.

OUTCOME

The Committee agreed to foreshadow the inclusion of pancreatic enzymes in Schedule 4 with no cut-off to lower schedules for the following reasons:

Contamination of Australian marketed pancreatic enzyme products with PPV and potential risk of human infection cannot be ruled out.

The available data suggest that the benefits associated with treatment of pancreatic exocrine insufficiency with porcine pancreatic enzymes outweighs the potential risk of PPV contamination of these products.

The risk-benefit ratio for the use of porcine pancreatic enzymes for conditions unrelated to pancreatic insufficiency, as OTC products or complementary medicines is too high, and those products should be withdrawn.

Foreshadowed for consideration at the February 2004 meeting

Schedule 4 - Amendment

PANCREATIC ENZYMES – amend entry to read:

PANCREATIC ENZYMES

16. OTHER MATTERS FOR CONSIDERATION

16.1 AMINOLEVULINIC ACID

PURPOSE

The Committee considered the scheduling of aminolevulinic acid.

BACKGROUND

The scheduling of the methyl ester of aminolevulinic acid, methyl aminolevulinate, an antineoplastic agent, was considered by the Committee at the June 2003 Meeting and was include in Schedule 4 on the grounds that the condition being treated required medical diagnosis, patient management and monitoring by a medical professional.

The Secretariat received a public inquiry seeking advice on whether aminolevulinic acid was a derivative of methyl aminolevulinate under the provision specified in Part 1-Interpretation, Paragraph 2(c) which states that “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." The matter was referred to the Committee for an interpretation.

DISCUSSION

Members were advised that aminolevulinic acid is a natural biological substance produced by all humans. It was noted that the substance was available in other countries as a therapeutic agent with sufficient toxicity to warrant scheduling if it were to be marketed in Australia.

The Committee did not consider that aminolevulinic acid was a derivative of methyl aminolevulinate and as such was not included in Schedule 4. Furthermore, in the absence of any products containing aminolevulinic acid on the Australian market and information on its use, the Committee considered it appropriate to wait until a submission for registration containing a full data package was received before considering the scheduling of aminolevulinic acid.

OUTCOME

The Committee agreed that aminolevulinic acid should remain unscheduled at this time.

16.2 IBUPROFEN AND CODEINE

PURPOSE

The Committee considered correspondence from XXXXXXXXXX concerning XXXXXXXXXX.

BACKGROUND

XXXXXXXXXX purchases made by a consumer of XXXXXXXXXX, a Schedule 3 product, from several pharmacies. XXXXXXXXXX is a combination of ibuprofen (200 mg) with codeine phosphate (12.8 mg).

OUTCOME

The Committee noted the correspondence from XXXXXXXXXX.

16.3 1,4-BUTANEDIOL, GAMMA AMINOBUTYRIC ACID, GAMMA BUTYROLACTONE, GAMAHYDROXYBUTYRALDEHYDE AND RELATED ANALOGUES

PURPOSE

The Committee considered correspondence from XXXXXXXXXX concerning 1,4-butanediol and related analogues.

BACKGROUND

The scheduling of 1,4-butanediol, gamma aminobutyric acid, gamma butyrolactone, gamma hydroxybutyraldehyde and related analogues and metabolic precursors was considered at the June 2003 Meeting. The Committee agreed to recommend to XXXXXXXXXX that the following substances be considered for inclusion in the XXXXXXXXXX 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.

XXXXXXXXXX advised that their Code of Practice for Supply Diversion into Illicit Drug Manufacture had been amended to include the substances listed above.

OUTCOME

The Committee noted that correspondence received from XXXXXXXXXX. Members were appreciative of the speed with which XXXXXXXXXX actioned the Committee's request.

17. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

17.1 DROMETRIZOLE TRISILOXANE

PURPOSE

The Committee considered the scheduling of drometrizole trisiloxane.

BACKGROUND

XXXXXXXXXX sought approval for drometrizole trisiloxane to be used as a UV filter in listed sunscreen products. MEC noted that drometrizole derivatives had been used widely in polymer photo-protection for the past 40 years and their photochemistry has been extensively studied. Drometrizole trisiloxane had been on the accepted list of UV filters in the European Union since September 1998, at a concentration of up to 15% in sunscreen products.

DISCUSSION

The Committee noted the following points raised in the MEC minutes:

- Drometrizole trisiloxane exhibits low acute toxicity (LD_{50} >2000 mg/kg) in acute oral and dermal toxicity studies in rats and mice. These results were attributed to the very low systemic exposure following oral and dermal administration. Intraperitoneal administration to rats produced moderate to low toxicity, with LD50 values of 563 mg/kg in female and 2000 mg/kg in male rats, and 1200 and 2000 mg/kg in female and male mice, respectively. No obvious reason for the pronounced sex difference observed with both species was noted. There were no changes of toxicological significance in repeat dose oral toxicity studies in rats at up to 1000 mg/kg/day and mice. Testing at higher dosages was thought to be unnecessary since kinetic data showed that increasing the dose did not lead to a relative increase in exposure.
- The reproductive toxicity NOEL was estimated to be 1000 mg/kg/day, based on studies on rats and rabbits. While one study showed an equivocal result for developmental changes in chinchilla rabbits, this was thought to be an aberration as there was no evidence of similar results in the repeat study with rabbits or in rat studies.
- *In vitro* studies using bacterial and mammalian cell systems and *in vivo* studies in mice showed no evidence of genotoxicity. However, information regarding whether drometrizole trisiloxane can penetrate cells to interact with genetic material is not available.
- While a carcinogenicity bioassay was not provided in the MEC submission, two expert commentaries were provided as justification for the absence of this test. The XXXXXXXXXX XXXXXXXXXX concluded that, based on the available information in support of the application, the likelihood of drometrizole trisiloxane being carcinogenic would be low to negligible.
- Toxicokinetic data in rabbits, mice and rats indicates that the systematic exposure following oral or dermal administration of drometrizole trisiloxane is very low (< 1%). Metabolism of the parent molecule is limited or unlikely, with no sex differences or likely accumulation observed in rats. An *in vitro* test for percutaneous absorption using human skin *ex vivo* found that approximately 0.8% of the amount applied to the skin was absorbed. Two studies measuring *in vitro* percutaneous absorption using human skin reported values of less that 0.5% and 0.32%.
- Drometrizole trisiloxane is not an ocular irritant in rabbits and was not found to be a skin irritant nor a sensitising agent in the animal models studied. It was not phototoxic or photosensitising in guinea pigs at concentrations up to 85%.
- Human studies indicated that drometrizole trisiloxane is not a skin sensitiser in normal and atopic agents. It is not phototoxic and did not induce photoallergenic reactions in humans. A sunscreen containing XXXXXXXXXX drometrizole

trisiloxane did not show comedogenic potential and was deemed unlikely to have an adverse effect on normal human skin.

The Committee agreed that the low toxicity of the drometrizole trisiloxane warranted exemption from scheduling requirements.

The Committee considered whether it was appropriate for all new active substances for use in sunscreen products being considered by the TGA to be referred to the NDPSC for consideration of scheduling. A member advised that the Committee should continue to review new active substances of this type so as to maintain consistency. Furthermore, it was felt that the review of new sunscreens was warranted on the basis that they are applied to large areas of the skin thus resulting in a large exposure despite having a low toxicity. A member advised that the review of all new active sunscreen substances was unlikely to cause a significant increase in workload for the NDPSC. The Committee agreed that all new active substances for use in sunscreens reviewed by the TGA should be referred to the Committee.

DECISION 2003/39 - 39

The Committee agreed to exempt drometrizole trisiloxane from scheduling on the basis of low toxicity and included it in Appendix B under category 6.4 – sunscreen.

Appendix B – New Entry

DROMETRIZOLE TRISILOXANE ……..October 2003……..a……..6.4

18. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

18.4 SEDATING ANTIHISTAMINES/CODEINE

PURPOSE

The Committee considered the scheduling of combined antihistamine preparations containing other active ingredients, including paracetamol, codeine and pseudoephedrine.

BACKGROUND

In Australia, primary entries for antihistamines were in S4, sedating oral antihistamines in S3 and non-sedating antihistamines including compounded non-sedating antihistamines in Schedule 2 (S2). In contrast, all antihistamines in New Zealand (NZ) were included in Part III (S2). The inclusion of single active sedating antihistamine products in S3 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) was based on concerns that such products were inappropriately used for sedation, particularly of infants and children.

The June 2003 NDPSC meeting endorsed TTHWP Decision 8/8 with the following proposed amendments, and referred this decision to NZ for consideration:

- Antihistamines and preparations with the potential for serious abuse be included in S4/Part 1;
- Single-active preparations of sedating antihistamines be included in S3/Part II; and
- Single-active preparations of non-sedating antihistamines and specified combination preparations of antihistamines be included in S2/Part III.

DISCUSSION

Following the June 2003 meeting, the NDPSC received an inquiry from NZ-MCC, seeking clarification regarding the intent of TTHWP Decision 8/8. It was highlighted that the amendments relating to Decision 8/8 would reclassify a significant number of existing oral sedating antihistamine products in combination with analgesics such as paracetamol from S2 to S3, in NZ. In addition, NZ also raised the issue that there were S2 products registered in both NZ and Australia containing a combination of sedating antihistamines, paracetamol and codeine.

Data on combination products containing paracetamol, codeine and antihistamines registered on the ARTG were provided to members, which confirmed NZ's advice. Members also noted that the existing entries in the SUSDP for codeine did not allow codeine preparations compounded with antihistamines outside of S4 and similarly, the Schedule entries for sedating antihistamines did not allow preparations compounded with analgesics in S2. However, these provisions in the SUSDP were not reflected in the status of many combination products registered on the ARTG.

The Committee was notified that certain combination products containing codeine, paracetamol and sedating antihistamines were allowed under S2 in some States and Territories including XXXXXXXXXXX, which may have implications on uniformity of the regulation of such products between the jurisdictions.

Members were advised that consideration of the scheduling of antihistamines as recommended by NDPSC at the June 2003 meeting had been gazetted and included on the agenda of the November 2003 NZ Medicines Classification Committee (MCC) meeting.

The Committee agreed to foreshadow consequential amendments to the SUSDP for consideration at the February 2004 meeting to align the SUSDP with current regulation of antihistamines in the jurisdictions including NZ, and taking into account the following points:

- maintain the status quo of existing day and night cough/cold/flu preparations containing sedating antihistamines for night time doses and labelled as S2; and

- remove the specificity from existing sedating antihistamine entries in the SUSDP to allow the inclusion of wider range of substances in combination antihistamine preparations, where considered appropriate at registration.

OUTCOME

The Committee agreed to foreshadow the following amendments to the SUSDP in order to align scheduling with the registration status of products while maintaining consistency with the recommendations of TTHWP Decision 8/8:

- All oral preparations containing non-sedating antihistamines, ie. single-active and compounded preparations combined with other S2 substances be included in S2;
- Allow oral combination preparations containing sedating antihistamines and other S2 substances formulated for night time dosing in S2.
- Oral sedating antihistamines combined with a S2 decongestant such as pseudoephedrine be allowed as S2.
- S2 codeine to be allowed in combined oral preparations containing an antihistamine in S2.
- All other oral sedating antihistamines be included in S3 except when included in Schedule 2.

Foreshadowed for consideration at the February 2004 meeting

Schedule 2 - Amendments

(sedating antihistamines - brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, diphenylpyraline, doxylamine and triprolidine):

[SUBSTANCE] – amend entry to read:

[SUBSTANCE] in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing [substance] in a night time dose,

except in preparations for the treatment of children under two years of age.

TRIMEPRAZINE – amend entry to read:

TRIMEPRAZINE in combination preparations for oral use when:

(i) compounded with a decongestant and not labelled for the treatment of children under two years of age; or

(ii) in a pack containing trimeprazine in a night time dose and not labelled for the treatment of children under two years of age,

except when included in Schedule 3.

(sedating antihistamines with indications other than for oral use):

PHENIRAMINE – amend entry to read:

PHENIRAMINE:

(a) in eye drops;

(b) in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing pheniramine in a night time dose,

except in preparations for the treatment of children under 2 years of age.

THENYLDIAMINE – amend entry to read:

THENYLDIAMINE:

(a) in nasal preparations for topical use;

(b) in combination preparations for oral use when:

(i) compounded with a decongestant; or

(ii) in a pack containing thenyldiamine in a night time dose,

except in preparations for the treatment of children under two years of age.

(amendment to allow codeine in combination with antihistamine)

CODEINE – amend entry to read:

CODEINE when:

(a) compounded:

(i) with a single non-opiate analgesic substance in tablets or capsules each containing 10 mg or less of codeine when:

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

(B) in a primary pack containing 25 or less dosage units; or

(ii) with a single non-opiate analgesic substance in individually wrapped powders each containing 10 mg or less of codeine when in a primary pack containing 25 or less dosage units; or

(iii) with one or more other therapeutically active substances:

(A) in divided preparations each containing 10 mg or less of codeine; or

(B) in undivided preparations containing 0.25 per cent or less of codeine; and

(b) labelled with a recommended daily dose not exceeding 60 mg of codeine.

19. INITIAL REVIEW/FORMAL OPINIONS (PHARMACEUTICALS)

22.1.1 3,4-METHYLENEDIOXY-N,A-DIMETHYLPHENYLETHYLAMINE (MDMA)

The Committee was advised that the nomenclature for 3,4-methylenedioxy-N,a-dimethylphenylethylamine (MDMA) in Schedule 9 of the SUSDP may be incorrect.

A member advised that the World Health Organization chemical name for MDMA based on the WHO list (Part One – Psychotropic Substances under International Control), is (+/-)-N,α-dimethyl-3,4-(methylenedioxy)phenylethylamine. There was no INN for this illicit drug.

OUTCOME

The Committee agreed to foreshadow consideration of the following amendment at the February 2004.

Foreshadowed for consideration at the February 2004 meeting

Schedule 9 – Amendment

3,4-METHYLENEDIOXY-N,α-DIMETHYLPHENYLETHYLAMINE – amend entry to read:

(+/-)-N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).

24. ATTACHMENTS

ATTACHMENT 1 - NICOTINE IN NRT SUMMARY OF POST-MEETING COMMENTS – ITEM 1.8.1.3.7

The XXXXXXXXXXX raised the following points:

- Utilisation of services for treating dependence on tobacco-delivered nicotine was extremely low in Australia, where smokers underestimated the usefulness of aids to smoking cessation. Some smokers who were unsuccessful in quitting smoking following the use of pharmacotherapy products failed to make the necessary attitude and environmental adjustments and were over-confident of the usefulness of such products.
- Moving NRT to general sale could lead to reduced confidence in the product and loss of some of the "placebo" benefit. In addition to NRT, availability of behavioural counselling and support is essential for a successful quit attempt.
- Consideration of scheduling of NRT and subsidy of tobacco dependence treatments should take into account broader government policy and strategies for smoking cessation.

- Noting these concerns, XXXXXXXXXXX stated that it would support rescheduling of NRT currently in Schedule 2 to general sale, provided the following recommendations were adopted:
  - QUITline and other support services be promoted in educational materials, eg. Consumer Medicine Information (CMI), to be made available at the point-of-sale which should emphasise the limitations of NRT to avoid unrealistic expectations placed on such products.
  - Enhance the capacity of QUITline services across Australia and broaden the availability of smoking cessation programs.
  - Increase referrals to the QUITline through targeted advertising and promotions.
  - NRT products at discounted prices should be made available to smokers on low-income and who are contraindicated to XXXXXXXXXXX.
  - Fund Aboriginal health services, drug treatment agencies and other federally funded health services to allow availability of cheaper NRT products to service clients.
  - Independent study should be undertaken to evaluate usage rate and efficacy of NRT in relation to where the products were purchased.
  - State and Territory Governments to implement measures to enhance the rate of smoking cessation by increasing access to smoking cessation aids and support programs in the jurisdictions. In addition, appropriate training should be provided

to healthcare workers and professionals involved in patient counselling and referrals.

- XXXXXXXXXXX indicated that there was a compelling public health case to de-schedule NRT based on the following arguments:

➢ A number of international recommendations, reports and research papers recognised that the potential public health benefit from NRT is determined by the level of access and usage rate. The World Health Organization (WHO) made a recommendation in 2001 to make NRT available, accessible and affordable for all smokers. A paper (McNeill et al.) that examined the regulation of NRT concluded that the current regulatory framework restricted access to NRT considering the likely consequence of continued dependence on a far more harmful, and widely available product: tobacco.

➢ The study commissioned by XXXXXXXXXXX identified that increasing access to NRT to include open sale in places such as supermarkets would increase use of products and quit attempts.

➢ Counselling and behavioural support increased the likelihood of successful smoking cessation attempts although NRT alone could be effective in aiding quitting, based on available evidence. However, such specialist support was already in place in Australia outside the pharmacy setting through cessation programs such as QUITline and quit groups.

➢ The WHO had reported that a number of studies had shown that NRT more than doubled abstinence rates compared to placebo in over-the-counter (OTC) use.

➢ If NRT gum and patches were to be de-scheduled, effective consumer information on the product label or in the product information (PI) should be available to consumers at the point-of-sale.

➢ The potential for misuse of NRT was low based on evidence from the United States and there was no evidence to support the claim that increased availability translated to increased risks.

➢ Existing regulatory framework surrounding nicotine gives the more harmful and highly addictive tobacco products a significant advantage in the marketplace over other nicotine delivery systems.

- XXXXXXXXXXX supported the exemption from scheduling of NRT products currently in S2 based on the following:

➢ products that deliver ‘clean’ nicotine should be more widely available than products that deliver nicotine in its most addictive and toxic form – cigarettes;

➢ NRT could be used safely while still smoking based on available evidence.

➢ XXXXXXXXXXX was working towards production of a short evidence-based video to encourage people to quit smoking which also provide advice on appropriate use of NRT.

- Draft national population health competency standards for training in the vocational education and training (VET) sector included units of competency in smoking cessation including use of pharmacotherapies. Provision of evidence-based training through the VET sector would result in a wider range of health workers with the capacity to provide support and advice on the use of NRT. XXXXXXXXXXX planned to provide training and accreditation over the next three years based on these competency standards for interested health professionals throughout the NSW health system.
- Information leaflets outlining the evidence for correct use of NRT, contraindications and contact numbers for support services should be co-located with products through general sale outlets such as supermarkets and general stores.

- XXXXXXXXXXX presented a summary of issues regarding the wider availability of NRT through non-pharmacy outlets, within the overall accepted national policy approach and strategy to reduce smoking in Australia. XXXXXXXXXXX provided the following comments:
  - Since the release of the XXXXXXXXXXX Report, literature searches were conducted but there remained no clear evidence that wider availability of NRT through supermarkets and other retail outlets reduced smoking prevalence.
  - In regards to the recommendations made by XXXXXXXXXXX, XXXXXXXXXXX would require funding from the Commonwealth to subsidise the cost of NRT programs, train counsellors on recommending the appropriate use of NRT and provide an infrastructure for the sale of NRT products. XXXXXXXXXXX was not resourced to introduce NRT programs and was unable to consider subsidising NRT schemes within the current forward estimates.
- XXXXXXXXXXX submission also raised the following issues:
  - Making NRT available from supermarkets may increase its accessibility but in isolation, would be inconsistent with Australia's current national tobacco policy. Existing policy deemed that pharmacological treatments should be combined with psychological treatments (eg. support counselling provided by a QUIT clinic) in order to achieve a long-term increase in quit rate. A recent article published in the Australian and New Zealand Journal of Public Health supported this approach in that NRT could increase chances of successfully quitting by 1.5-2 times, with efficacy increased when combined with other behavioural interventions such as counselling and support. Should NRT be made available over the counter through supermarkets, a minimum requirement would be that it should be offered in conjunction with rigorous cessation guidelines and a supporting consumer educational program.
  - Making NRT and cigarettes available from the same retail outlet could create the potential for smokers to use NRT continuing to use tobacco (eg. as a strategy to cope with workplace smoking bans). This could potentially undermine the status of NRT as a cessation product and raise issues about potential 'harm

minimisation' approach whereby NRT would be used to reduce the number of cigarettes smoked rather than for smoking cessation.

- XXXXXXXXXXX was concerned that unregulated use could result in the potential for inappropriate and unregulated use by the general population, in particular children and pregnant women. Whilst NRT may be considered a safer option to cigarettes, there was a lack of research and evaluation available on the effects of NRT on pregnant and lactating women.
- A decision to down-schedule may diminish XXXXXXXXXXX ability to address issues of price as a barrier to access in that it could mitigate against NRT ever being reconsidered for listing on the Pharmaceutical Benefits Scheme (or subsidised in some other form based on the experience of other developed countries such as the UK and NZ).
- There was a lack of available rigorously evaluated cessation guidelines and consumer education on the use of NRT. The Australian policy on NRT supports its use as a short-term aid to smoking cessation, not as a long-term alternative to smoking.
- Because NRT forms one part of a multi-faceted tobacco control strategy, XXXXXXXXXXX maintained that any change to scheduling of NRT should ideally be made in the context of a broad tobacco control strategy. XXXXXXXXXXX continued to have the reduction of harm caused by tobacco, as one of its public health priorities and promoting cessation of tobacco was one key strategy area. XXXXXXXXXXX would continue to monitor the NZ model and other international developments in this area.

- XXXXXXXXXXX; and XXXXXXXXXXX in a joint pre-meeting submission supported the recommendations of XXXXXXXXXXX. Availability of NRT to smokers living in remote regions where access to GPs and pharmacy services was limited was also highlighted as an issue.
- XXXXXXXXXXX supported wider availability of NRT and stated that trained health staff in XXXXXXXXXXX should be given the ability to offer NRT to nicotine dependent clients.
- XXXXXXXXXXX XXXXXXXXXXX XXXXXXXXXXX recognised that exemption from scheduling of NRT products would increase access to an effective anti-smoking treatment and that behavioural counselling or support played an essential role in successful smoking cessation. XXXXXXXXXXX proposed that patches, gum and lozenges should be of similar scheduling based on similarity in safety profiles and product format. XXXXXXXXXXX XXXXXXXXXXX XXXXXXXXXXX XXXXXXXXXXX XXXXXXXXXXX.
- XXXXXXXXXXX submitted a pre-meeting application to exempt all NRT products from the requirements of scheduling to allow the same level of availability as cigarettes and tobacco in supermarkets and other retail outlets. They stated the following as the key reasons in support of their application.

- Supermarkets could make NRT available at a cheaper price, which would encourage more smokers to use the products. NRT products were widely available in overseas markets including New Zealand, the United States and the United Kingdom and there were no safety issues identified.
- Nicotine in transdermal patches and gums were available front-of-shop in pharmacies where pharmacist intervention was not required at the point-of-sale. It was unlikely that pharmacy assistants would be able to appropriately screen potential users with contraindications from purchasing NRT products, and this scenario would be similar in supermarkets.

- XXXXXXXXXXX in a pre-meeting submission supported the appropriate deregulation of restriction on access to medicines in Australia and recommended that scheduling decisions must be based on evidence.
- XXXXXXXXXXX supported the status quo on the grounds that safe use of NRT and successful outcomes could be enhanced where access to professional advice was available at the point-of-sale. XXXXXXXXXXX had been involved in developing a range of pharmacy resources to help deliver information, support and counselling associated with the supply of smoking cessation products.
- XXXXXXXXXXX submitted a late paper to the NDPSC opposing the de-scheduling of NRT products for general sale and stated that harmonising with New Zealand was inappropriate for the following reasons:
  - The WHO recognised that support for the treatment of tobacco dependence required a range of interventions including behavioural and counselling and that the success of such interventions depended on their synergistic use in a broader context of a comprehensive tobacco-control strategy. De-scheduling of NRT may be inconsistent with the WHO Framework Convention on Tobacco Control which Australia was expected to sign by the end of 2003. The community pharmacy initiatives which included the implementation of professional standards and accreditation assessment were consistent with the WHO policy direction.
  - Availability of NRT in non-pharmacy outlets would direct consumers away from professional support required to achieve good health outcomes and would likely result in increased prices.
  - Scheduling and subsidy of tobacco dependence treatments should be considered within the context of broader government policy and strategies.
- XXXXXXXXXXX in a pre-meeting submission stated that scheduling recommendations and decisions should be based on clear clinical evidence. XXXXXXXXXXX was of the view that the public health benefits of enhancing access to NRT through down-scheduling, and removing requirements for professional advice in such medications was outweighed by the public health risks involved in such a move. There were clear contraindications and side-effects of NRT which were yet to be adequately addressed through appropriate labelling and consumer information. Continued dispensing through pharmacists would help address these

important health issues by ensuring that appropriate counselling and advice was available to the consumer.

- XXXXXXXXXXX, a sponsor of NRT products listed on the ARTG, supported rescheduling of NRT provided that such a decision was based on evidence.

ATTACHMENT 2 - LEVONORGESTREL SUMMARY OF POST-MEETING COMMENTS – ITEM 12.1

- XXXXXXXXXXX – As the sponsor, mentioned that the primary data for XXXXXXXXXXX and pivotal studies which were requested by our evaluator were provided to TGA in support of the original application to register XXXXXXXXXXX. The company commits to ensuring the provision of adequate training and educational materials for pharmacists, advice about the risk of ectopic pregnancy, adverse effects and need for medical management.
- XXXXXXXXXXX put forward some comments in relation to the June 2003 NDPSC Meeting Record of Reasons.
- XXXXXXXXXXX supported the decision for the reasons of a high abortion rate in Australia, low toxicity of progestogen-only EPC (an increased risk of thromboembolism to oestrogen containing EPC but not to progestogen-only EPC), requirement for timely access to EPC.
- XXXXXXXXXXX supported the decision. Pharmacy dispensing of EPC has been demonstrated to be satisfactory by users in Britain.
- XXXXXXXXXXX strongly supported the decision. Women in both the metropolitan and rural and remote areas will be benefit from it. It is expected that the abortion rate (8000/year in XXXXXXXXXXX) may be reduced by ~25% due to the S3 access to ECP.
- XXXXXXXXXXX supported for the reasons raised in the original submission.
- XXXXXXXXXXX, XXXXXXXXXXX, XXXXXXXXXXX stated that XXXXXXXXXXX welcomed the decision, and suggested the provision of written information to include advice on ongoing contraception, access to testing for STDs and also recommended medical review and ongoing follow up to exclude pregnancy.
- XXXXXXXXXXX supported the decision as an important positive step towards decreasing the rates of unintended pregnancy, in particular in teenagers. There is no evidence that young people abuse its OTC availability.
- XXXXXXXXXXX, XXXXXXXXXXX strongly supported the decision. Significant public health benefits included more timely access to the medication for women, especially for those in rural, regional and remote areas. The listing of levonorgestrel in Appendix H was also supported for the purpose of enhancing women's awareness of its availability.
- XXXXXXXXXXX applauded the Committee's decision which in her view would assist in reducing the number of unintended pregnancies in Australia. The following points were submitted:

  - Ready access to EPC is paramount for its efficacy;
  - GPs may not be available for emergency contraception, especially on weekends, in rural and remote area, or a moral or religious objection by the practitioner;

- Studies in the USA and UK showed that access to EPC does not adversely affect use of routine contraception;
- Most women are able by reading the label to understand the key information necessary for safe and effective use of OTC progestogen-only EPC;
- Available information should include method of use, when to have a pregnancy test or STD check, safe sex and other regular contraceptive options.

- XXXXXXXXXXX made the follow recommendations:
  - Vary the recommended amendment to the SUSDP and improve the timely access by advance prescription, call by pharmacist to doctor for consultation and prescription, and/or emergency medical appointment.
  - Sets aside the amendment to enable the consultation with XXXXXXXXXXX of Australia and other stakeholders to develop a satisfactory resolution to the nature and circumstances of the counselling required for S3 medications.
- XXXXXXXXXXX opposed the decision based on the following claims:
  - Concern regarding the risk of ectopic pregnancy based on the drug's mechanism of action;
  - There was no evidence to support the contention that the availability of levonorgestrel for EC had any effect on abortion rates;
  - The potential exposure of teenagers to the risks associated with the use of levonorgestrel and the absence of an effective mechanism to prevent the provision of the drug to females under 16 years of age;
  - The issues relating to privacy, toxicity (teratogenic effects, developmental adverse effects to females under 16), contraindications (high blood pressure, existing pregnancy, age under 16) and the potential for abuse had all remained unresolved.
  - It was submitted that the decision is not consistent with the usual requirement for 2 years of local clinical use, since levonorgestrel had only less than 12 months of local clinical use, 16 and 13 months as an OTC product in the UK and NZ respectively. In contrast, the regular contraceptive pill with the same substance taken in much lower doses, will continue to require a prescription.
- XXXXXXXXXXX opposed the decision due to concerns about thromboembolic side effects, possible deaths as a result of taking the contraceptive pill, and encouraging irresponsible sexual behaviour. Having to see a doctor will reduce the use of "Morning-after pills".
- XXXXXXXXXXX argued about the concept of "abortifacient" in the Record of Reasons, based on embryology-based terminology.
- XXXXXXXXXXX opposed the down-scheduling decision, and pointed out that levonorgestrel can act post-conception. The following points were submitted:

- The contraindications stated in the manufacturer's Product Information (PI) had not been given adequate consideration by the NDPSC. These included severe hypertension (BP >180+/110+), diabetes mellitus with nephropathy, retinopathy, neuropathy or vascular disease, ischaemic heart disease, stroke, or a past history of breast cancer. It is stated in the product information that "in individual cases, the risk-benefit ratio should be assessed by the practitioner in discussion with the patient". Furthermore, the manufacturer asserted that XXXXXXXXXXX should not be given to pregnant women and that the exclusion of early pregnancy required pathology testing.
- Lack of evidence to demonstrate the benefits from increased availability of levonorgestrel.
- Pharmacies do not have the facilities required to provide confidential counselling to women.
- It was submitted that the Committee accepted claims that appropriate information would be available via consumer medicine information (CMI). However, CMI is irregularly provided or incorporated by pharmacists, and a woman using levonorgestrel is unlikely to give much attention to the CMI. The women has a right to have full information, an informed consent based on the knowledge in the mechanism of the drug. In addition, the risk of ectopic pregnancy was not mentioned in the CMI.
- Levonorgestrel will be accessed OTC, while other pharmaceutical contraceptive options require a prescription.
- Potential for abuse by teenagers: the data indicate increased usage of morning-after pill from 1 in 12 to 1 in 5 teenage girls since it became available over the counter in the UK, and also teenagers are the most frequent users of emergency contraception at Australian Family Planning Clinics. There is potential for using to cover up for sexual abuse.

- XXXXXXXXXXX expressed concerns on safety, easy availability to teenagers, issue of abortifacient/early abortion, proliferation of sexually transmitted diseases (STDs, having easy sex without being prepared) and available consultation in pharmacies (a pharmacy assistant rather than a pharmacist ultimately distribute the product).
- XXXXXXXXXXX submitted that the decision to dispense levonorgestrel OTC will promote promiscuous sexual practices and could lead to serious social and health (transmission of sexually transmitted diseases) problems.
- XXXXXXXXXXX opposed the decision, and expressed concerns on early abortion by levonorgestrel and resulting psychological trauma. Since the correspondent was involved in the S2/S3 program and the XXXXXXXXXXX Program, he pointed to a claimed lack of care and advice to customers, and fallen standards due to understaffed pharmacy stores. He was also concerned at the legal implications for the pharmacist in case of an ectopic pregnancy or a malformed baby after levonorgestrel treatment (will the sponsor company be liable?)

- XXXXXXXXXXX – Expressed concerns over issues including increased abortion rates (taking the drug as an abortifacient) and relevant mental illness rates, sexual promiscuity among teenagers and STDs, as well as adverse effects related to long term or multiple use of this product.
- XXXXXXXXXXX opposed the decision and made a claim that the Committee had failed to demonstrate that the drug would not detrimentally affect women's health, both generally and emotionally. An argument was also presented on the concept of "abortifacients", and its interpretation by TGA.
- XXXXXXXXXXX opposed the decision, and submitted concerns on:
  - Illegality. It was submitted that the intention in taking the pill is to procure a miscarriage in that it is intended to prevent implantation of a human embryo in the lining of the uterus of the woman. No State in Australia allows a pharmacist to supply this drug with the intention of procuring a miscarriage. It is beyond the power of the Committee to authorise the dispensing of this drug by pharmacists.
  - Concealing a serious offence involving underage buyers. It was submitted that under all State laws, it is an offence for someone to have sexual intercourse with a female under a particular age (usually 16 yr). Therefore, a pharmacist supplying levonorgestrel to someone under 16 years of age would be required to disclose to Police certain personal details of the person who made the purchase. On this basis, the Committee is bound to limit the access to the drug to girls older than 16 years.
- XXXXXXXXXXX, a pregnancy help counsellor and a medical adviser for the book XXXXXXXXXXX XXXXXXXXXXX XXXXXXXXXXX XXXXXXXXXXX) opposed the rescheduling, and discussed the risks and benefits associated with the use of the product.
  - It was submitted that the potential teratogenicity was understated in the product information (PI) for XXXXXXXXXXX, and that the OTC availability of XXXXXXXXXXX would lead to large doses of levonorgestrel being taken without prior testing for pregnancy. The PI for XXXXXXXXXXX is contradictory stating "the consensus is that levonorgestrel is not teratogenic" then later stating "progestogens such as levonorgestrel can cause virilisation of the female fetus. This is a dose dependent effect". It was submitted that fifty tablets of levonorgestrel 30mcg, which would be equivalent to XXXXXXXXXXX, would have a greater teratogenic effect.
  - It was submitted that the product information repetitively stated the lack of studies, or lack of data. XXXXXXXXXXX is likely to be accessed by girls aged 14-16 years, who may be at risk of serious long-term side effects.
  - It was submitted that some of the serious potential side effects and contraindications listed in MIMS for "XXXXXXXXXXX" XXXXXXXXXXX (30 mg levonorgestrel) were ignored or understated in the PI for XXXXXXXXXXX.

- It was submitted that easy access to XXXXXXXXXXX would encourage sexual promiscuity. Studies in GHANA (Lovvorn et al, 2000) indicated that the availability of EPCs increased the frequency of unprotected intercourse.
- It was submitted that since a pharmacist does not keep a record of consumers who had purchased S3 medicines, the pharmacist is unlikely to prevent repeated use of XXXXXXXXXXX and women could potentially be exposed to large amounts of levonorgestrel over many years without her doctor being aware.
- The down scheduling will lead to shifting of medico-legal responsibility to pharmacists, the drug company, and potentially the TGA.

- Drs XXXXXXXXXXX, XXXXXXXXXXX and XXXXXXXXXXX, XXXXXXXXXXX opposed the decision and expressed similar concerns as the above regarding teratogenicity and its potential liability (thalidomide as an example), potential side effects/contraindications, increased cardiovascular disease, breast cancer and cervical cancer risk, safeguards to prevent teenager overuse, misuse and for teenagers already pregnant. The estimation by the sponsor that XXXXXXXXXXX prevents 85% of expected pregnancies suggests that about 15% of pregnancies continue, and this potentially means large numbers of babies exposed to high levels of levonorgestrel.
- A number of similar submissions were received which opposed the rescheduling of levonorgestrel EC based on moral and ethical grounds.

(The following submissions were from those who did not make a pre –meeting submission and therefore, did not comply with regulation 42ZCZ of the Therapeutic Goods Regulations 1990.)

- XXXXXXXXXXX supported the decision for the reason of easy access, and suggested its inclusion in the PBS.
- XXXXXXXXXXX supported the decision and further suggested:
  - To include levonorgestrel in Appendix H of the SUSDP.
  - Put education and monitoring programs in place, and collect data to measure its impact.
  - Permit nurse practitioners to distribute EPC, and include EPC in the PBS, in order to promote its use in rural and remote areas.
- XXXXXXXXXXX It was submitted that 'vulnerable' women and street kids involved in prostitution were susceptible to overuse of levonorgestrel and it was highly likely that pharmacy assistants, rather than pharmacists, would be involved in the sale of what was considered a 'high risk' drug. It was submitted that an S3 availability was not appropriate given the increased public concern regarding the dangers of deep vein thrombosis, pulmonary embolism, stroke and the increased risk of ectopic pregnancy. XXXXXXXXXXX stated that deaths had occurred overseas as a result of the ingestion of drugs of this nature.

- XXXXXXXXXXX opposed the decision. It was submitted that the mechanism of the drug is to prevent implantation. Medical advice is necessary for the following reasons.
  - Two Morning-after Pills contain fifty times the dose of levonorgestrel in the XXXXXXXXXXX (750 mg *vs* 30 mg). According to MIMS, contraindications of XXXXXXXXXXX (hence XXXXXXXXXXX) consist of thrombophlebitis or thromboembolic disorders, cerebrovascular or coronary artery disease, known or suspected carcinoma of the breast/genital organs, oestrogen dependent neoplasia, pregnancy/a history of herpes of pregnancy, hepatic dysfunction, severe diabetes with vascular changes. Levonorgestrel as an oral contraceptive may cause recurring exacerbation of conditions including depression, migraine or epilepsy, and cause some degree of fluid retention in conditions such as cardiac and renal insufficiency, migraine and asthma. It may cause serious cardiovascular side effects in cigarette smokers.
  - Britain's XXXXXXXXXXX had warned about the risk of ectopic pregnancies. XXXXXXXXXXX is a category D teratogen, and should not be given to pregnant women. Levonorgestrel is almost 100% bioavailable, and about 0.1% of the maternal dose can be transferred via milk to the nursing infant.
  - Severe malabsorption syndromes, such as Crohn's disease, drug interactions with barbiturates, primidone, phenytoin, carbamazepine, herbal medicines containing *Hypercicum perforatum* (St John's Wort), rifampicin, ritonavir, rifabutin and grisefulvin, might reduce or impair the efficacy of XXXXXXXXXXX and other levonorgestrel-containing medications.
  - Teenagers are the most frequent users of emergency contraception, but there is a lack of data about the impact of the drug on this group.
- XXXXXXXXXXX strongly opposed the decision. In a busy pharmacy, it is not possible to provide adequate time and privacy to allow appropriate counselling of clients. The buyer may be a male or parent, but not the patient. It was submitted that its OTC availability would convey to the consumer that it is "harmless", and could be used as a regular form of contraception.
- XXXXXXXXXXX opposed the rescheduling of XXXXXXXXXXX from S4 to S3. It was submitted that the organisation were concerned that:
  - There had not been adequate local trials or studies undertaken relative to the usage of this drug in Australia;
  - There were substantial risks of adverse reactions in the women most likely to be using this drug;
  - The provisions to properly provide for "informed consent" in the use of this drug were inadequate;
  - The integrity of the manufacturer of this drug was questionable;

- The goals in rescheduling levonorgestrel to allow OTC availability had not been made clear;
- The demonstration of "net public benefit" had not been made, and that the opposite effect may be the actual result; and legal liabilities for any harm that may occur were not clear and appeared to be in a current state of re-evaluation.

- XXXXXXXXXXX opposed the decision, and recommended that XXXXXXXXXXX remain in S4, in a similar fashion to the anti-retroviral drug XXXXXXXXXXX that also has variable efficacy after 72 hours following exposure, and currently requires prescription under NSW guidelines.
- XXXXXXXXXXX submitted concerns and opinions on the OTC of XXXXXXXXXXX.
  - It was submitted that the contraindications and precautions (based on manufacturer's prescribing information) that require history taking, medical examination and testing include: possibility of existing-pregnancy, severe hypertension, diabetes mellitus with nephrophthy, retinopathy, neuropathy, vascular disease, ischaemic heart disease, stroke, history of breast cancer, unexplained vaginal bleeding, hypersensitivity to any of the ingredients of the preparation, possibility of ectopic pregnancy if pregnancy occurs.
  - Drug interactions that warrant knowledge of other medications that the patient is taking: barbiturates, primidone, phenytoin, carbamazepine, phenylbutazone, rifampicin, ritonavir, ampicillin, griseofulvin and effects on the requirement for oral anti-diabetics and insulin.
  - Follow-up medical consultation (manufacturer's recommendation) for side effects, as a routine after 3 weeks, ongoing pregnancy due to failure, and ectopic pregnancy.
  - Ethically, women have a right to know that the abortifacient or anti-nidation effect is the most likely effect of XXXXXXXXXXX.
  - A need to determine whether an intervention by levonorgestrel is necessary by history taking or a serum hormone test, since a women is infertile most of the cycle.

ATTACHMENT 3 - IBUPROFEN SUMMARY OF POST-MEETING COMMENTS - ITEM 12.2

XXXXXXXXXXX was satisfied with the decision made in the June 2003 Meeting, and seeks to further clarify: 1) Only one of the three warning statements from Appendix F, 34 and 35 will be required in Schedule 2 – then Amended entry for ibuprofen; 2) Recent approval of the XXXXXXXXXXX label by the TGA/MEC is taken to be compliance with the scheduling requirements. XXXXXXXXXXX also provided remarks on recent media coverage relating to safety issues, including hospital admissions due to improper use of medicines; potential drug-drug interactions; contraindications; and aspirin-sensitive asthmatics. In addition, XXXXXXXXXXX submitted another letter (dated 7/10/2003) to comment on some media coverage, in particular, on a paper recently published in British Medical Journal (2003) regarding NSAIDs and the risk of miscarriage.

- XXXXXXXXXXX expressed their interest on the decision, and further presented a recent press release on the effect of ibuprofen in breast cancer. According to XXXXXXXXXXX, USA, long term use (5 years or longer) of low doses of ibuprofen is associated with a significantly decreased risk of breast cancer among postmenopausal women, probably by inhibiting cyclooxygenase-2 (COX-2). It was more effective than aspirin, and paracetamol was not protective.

- XXXXXXXXXXX did not support the decision. XXXXXXXXXXX submitted that the points listed in the Record of the Reasons in fact indicate that ibuprofen meets the criteria for S2. XXXXXXXXXXX submitted what it claimed was new evidence on the potential risk of ibuprofen.
  - It was claimed that a study in the UK found that the third most frequently implicated class was NSAIDs accounting for 12.5% of all drug-related admissions (76% for cardiovascular and central nervous system drugs).
  - It was claimed that a study in US revealed a relationship between NSAID use and miscarriage.
  - It was claimed that an increased risk of heart/renal failure is associated with the use of NSAIDs together with ACE inhibitors and/or diuretics (“triple whammy”).
  - It was claimed that a US survey showed that there was a high prevalence of analgesic use in the adult population, and a high rate of multiple analgesic use in females and younger age groups.
- XXXXXXXXXXX opposed the decision. XXXXXXXXXXX submitted a Newspoll study on the incidence of concomitant use of blood thinning medication and ibuprofen for pain relief, which included 604 males and females 45 years and over. On this basis, the following points were highlighted by XXXXXXXXXXX from the survey report:

- 43% of the total 604 patients were identified as being at risk of suffering a heart attack or stroke due to conditions including diabetes, high blood pressure, high cholesterol, previous heart attack or stroke.
- 26% of the total subjects stated that they took blood-thinning medication to prevent a heart attack or stroke, and from these 71% took aspirin products, and 29% took prescription and other products. 86% of the subjects who took blood-thinning medication also reported taking a pain relief medicine in the last 12 months.
- XXXXXXXXXXX submitted that in the last 12 and 3 months, 17% and 8% respectively of those taking aspirin to prevent a heart attack or stroke also took an ibuprofen product to relieve pain.
- XXXXXXXXXXX submitted that clinical studies have demonstrated that concomitant administration of ibuprofen antagonises the irreversible platelet inhibition induced by aspirin, thereby having a deleterious impact on its cardioprotective effects. XXXXXXXXXXX stated that the adverse event data from UK and USA directly associated with ibuprofen could not be considered satisfactory to substantiate a rescheduling to open sale status.
- XXXXXXXXXXX submitted that paracetamol is considered by specialists and other healthcare practitioners as first line treatment for mild to moderate pain. Paracetamol already has a wide distribution for immediate public access and there is no public health benefit to be gained by improving public access to a second-line medicine, which should be dispensed after professional consultation if paracetamol is considered to be inappropriate.
- XXXXXXXXXXX suggested that the decision be deferred for a period of a further 12 months during which time, more intensive and extensive research could be undertaken on the use of ibuprofen and its associated risks.
- In a letter to XXXXXXXXXXX (copy submitted), XXXXXXXXXXX expressed concerns that de-scheduling and allowing supermarket sales of ibuprofen will pose significant public health risks of side effects and complications.
- In the "Conclusions" section of its submission, XXXXXXXXXXX submitted that "the data contained in this report suggest, when extrapolated, that the deregulation of ibuprofen to an exempt from classification status may give rise to approximately 20,000 adverse events each year". XXXXXXXXXXX submission did not explain how this figure was derived and no details of the distributions of the nature or the severity of the claimed 20,000 adverse events were provided.

- An article recently published in Australian Pharmacist by Professor Gregory Peterson (University of Tasmania) expressed doubt on the strength of evidence presented in the PAIN study on which XXXXXXXXXXX believed the down-scheduling decision was based. The main points are summarised as the following:
  - There were considerable methodological deficiencies in the published PAIN study. In particular, the published paper did not include comprehensive inclusion

and exclusion criteria for patients included in the research study, there was no objective measurement of compliance with therapy reported and the patients were mainly young (mean average age of 43 years) therefore the results would not be applicable to the elderly. The fact that the PAIN study was funded by XXXXXXXXXXX raised the possibility of bias and doubts about the scientific and ethical integrity of any data produced.

- There was already a large body of literature on the gastrointestinal side effects of NSAIDs consistently showing that groups which had a markedly elevated risk of NSAIDs-induced gastrointestinal events included the elderly, persons with prior history of peptic ulcer disease and its complications, persons receiving anticoagulant or corticosteroid therapy, and persons who required long-term NSAID therapy, especially at high dosages.
- Information on recent (within the past week) use of multiple analgesics, plus data on tobacco, alcohol and other factors, were obtained from 627 patients enrolled in the American College of Gastroenterology (ACG) bleeding registry and from 590 procedure-matched controls. The risk of gastrointestinal bleeding was increased 2-3 fold among recent users of aspirin, ibuprofen and other NSAIDs at OTC doses, in a dose-related manner, based on these data. In contrast, no excess was found among paracetamol users.
- It had been documented that many pregnant women take ibuprofen at some point during the pregnancy without being aware of the potential risks. Its ready availability in supermarkets would simply reinforce the misguided perception that the drug is innocuous.

- XXXXXXXXXXX opposed the decision. The following points were raised:
  - XXXXXXXXXXX agrees with the Commonwealth Government that the use of the right medicine in the right patient for the right condition to achieve the right outcome is extremely important.
  - XXXXXXXXXXX survey showed that pharmacists do intervene in the sale of ibuprofen, a finding consistent with the S2/S3 standards. Professional intervention stops potential adverse events, stops drug interactions and is clearly contributing to the quality use of the product.
  - XXXXXXXXXXX submitted that not all pain states are the same and not all analgesics are appropriate for every pain state, nor are all analgesics appropriate for every patient (Therapeutic Guidelines, Analgesic, Version 4, 2002). XXXXXXXXXXX believe that without professional advice, the quality use of ibuprofen will be much reduced, and inappropriate uses and adverse consequences may occur.
  - XXXXXXXXXXX was concerned that the product label for exempt ibuprofen could have up to seven warning statements on each pack, some of which could be very serious, and if not read and understood by the consumer, could result in potentially fatal outcomes. For example, use in people taking warfarin or methotrexate.

- Responding to some statements in the Record of Reasons of the June 2003 Meeting, the following points were also submitted by XXXXXXXXXXX single doses of ibuprofen do inhibit the anti-platelet effect of low dose aspirin. 2) No solid data in Australia and overseas to rule out its effects on asthma, gastrointestinal and thrombotic events due to antagonism of low dose aspirin. 3) Ibuprofen is contraindicated in many patient groups eg. pregnancy, peptic ulcers, cardiac failure and aspirin sensitive asthma, where paracetamol may be used. There are more contraindications and drug interactions for ibuprofen than paracetamol. 4) The fact that "the safety of low dose ibuprofen in the OTC setting is good" may be due to the intervention of the pharmacist, but may be lost if it was sold in non-pharmacy outlets.
- XXXXXXXXXXX asked the NDPSC to give fully referenced feedback on issues raised in this submission and in its previous letters to the Committee.

- XXXXXXXXXXX was disappointed at the decision, and submitted the following points in response to the reasons for the decision:
  - There is no evidence to suggest that greater availability and unsupervised sale of ibuprofen is warranted.
  - That the statement "without any increase in the incidence of adverse effects for general sale of ibuprofen in the USA and UK" had not been substantiated by the Committee. It was claimed that a study in USA in 1990-1992 indicated that OTC NSAIDs use may represent a more important cause of peptic ulcer disease and ulcer-related haemorrhage than previously appreciated. Similarly in a UK study, an estimation of 12.5% of drug-related hospital admissions were due to NSAIDs of which ibuprofen and diclofenac were most commonly implicated.
  - The fact that significant risks are associated with the indiscriminate use of aspirin and paracetamol should be a basis for stricter scheduling of ibuprofen, rather than for the addition of a third agent of this type, unless the latter shows an apparent superior safety profile.
  - Australian OTC marketing experience (S3 and S2) with ibuprofen can not be extrapolated to predict its safety as an unscheduled medicine.
  - It was submitted that reliance cannot be placed on package labelling to adequately inform consumers on the use of this medicine. For example, a study in 578 pregnant women in rural USA showed that despite package labelling, 15% of these women took OTC ibuprofen at sometime during the pregnancy, and 5.7% during the third trimester.
  - If ibuprofen is unscheduled, there is clearly no personalised, professional advice on the appropriate use of medicines which occurs in the pharmacy setting.

- XXXXXXXXXXX strongly opposed the June 2003 decision relating to ibuprofen. XXXXXXXXXXX supported its submission with one volume of references, which was assessed by the Clinical Pharmacologist, who reported the evaluation outcome to the meeting. The following points were included in the submission:
  - It was submitted that 17-26% of purchasers of OTC analgesics are aged 50 years or older who are likely to have other medical conditions. The Prescribing Information for current prescription-only ibuprofen products XXXXXXXXXXX and XXXXXXXXXXX suggests that caution should be taken even when used in the elderly at low prescription doses of 1200-1600 mg.
  - 34% of purchasers are women aged between 18 and 39 years. It was submitted that new data published in British Medical Journal (2003) indicates that use of either ibuprofen or naproxen during pregnancy or around the time of conception increased the risk of miscarriage by 80% or higher.
  - In addition to headache, primary conditions related to the potential use of ibuprofen include back and neck pain that requires treatment 1.5 days per week on average, migraine, joint pain, muscular pain and dysmenorrhoea with a varied frequency of suffering.
  - It was submitted that based on the NDPSC June 2003 meeting decision, there would be seven label warning statements (asthma, stomach ulcers/disorders, allergy to ibuprofen, impaired kidney function, heart failure, pregnancy, concomitant medications) on the packet. Would they be too many for a medicine on supermarket shelves? Would more be required?
  - It was submitted that case reports showed that a single OTC dose of ibuprofen can cause a fatal asthma attack. In addition, a group of ~ 20% asthmatics are sensitive to aspirin/ibuprofen, and the average age of appearance of NSAID-induced asthma was in the early 30s.
  - It was submitted that the anti-platelet, cardioprotective effect of low-dose aspirin may be blocked by a single OTC dose of ibuprofen, which could lead to increase in both overall and cardiovascular mortality.
  - It was submitted that recent USA reports indicate increased incidence (by 20%) of GI bleed, including over 100 hospitalisations (5 deaths and 12 life-threatening GI complications) directly associated with OTC doses of ibuprofen.
  - It was submitted that the pack size of 25 dose units (for 4.17 days treatment) is inconsistent with the current warning statement for OCT ibuprofen "if symptoms persist for more than 3 days, consult a doctor", or with packs of unscheduled paracetamol and aspirin (25 tablets for 3 days treatment).
  - It was submitted that the anti-inflammatory effects of ibuprofen only appear at >1200 mg/day, but not at OTC doses.

(Submissions from those who did not make a pre –meeting submission and therefore, did not comply with regulation 42ZCZ of the Therapeutic Goods Regulations 1990.)

- XXXXXXXXXXX did not support the rescheduling based on the following concerns:

  - The recent Review of Non-prescription Analgesics by the Medicine Evaluation Committee referred to this: "While each of the three main non-prescription analgesics – paracetamol, aspirin and ibuprofen – can be considered individually, the controls on them must not be seen in isolation. Restrictions on one will result in substitution with another and the advantages and disadvantages of the substitution must be contemplated by public health authorities." XXXXXXXXXXX takes the view that the Committee needs to be cognisant of the broader picture, when considering the down-scheduling of ibuprofen.
  - XXXXXXXXXXX expressed concern at the possibility of patients doubling up on doses of NSAIDs to produce gastrointestinal disturbance, with ulceration and haemorrhage being more serious complications. Pharmacists frequently find that patients requesting ibuprofen are already taking a prescribed NSAID including ibuprofen itself. Counselling of consumers prior to purchasing ibuprofen should be maintained within the pharmacy setting.
  - The issue of drug interactions, including so-called "triple whammy", a combination of diuretics, ACE inhibitors and NSAIDs, has become more pressing. The elderly are more at risk of this complication, since they are naturally more likely to seek a non-prescription medicine for arthritic pain while they are receiving concomitant cardiovascular medication.
  - XXXXXXXXXXX advised that it was so concerned with the matter that it would give consideration to approaching the XXXXXXXXXXX with a view to recommending the amendment not taking effect in this State, despite the obvious disadvantages of non-uniformity of scheduling.

- XXXXXXXXXXX expressed concerns on potential drug interactions and inappropriate use of ibuprofen and other NSAIDs. For example, a patient requested for XXXXXXXXXXX for a joint pain, and further asked for some XXXXXXXXXXX for headache, with the intention of taking both concurrently.

- XXXXXXXXXXX did not support the decision, and emphasised the role of pharmacists in ensuring the safe use of XXXXXXXXXXX.

- Some individual pharmacists (XXXXXXXXXXX; XXXXXXXXXXX; XXXXXXXXXXX; XXXXXXXXXXX; XXXXXXXXXXX; XXXXXXXXXXX) submitted comments to express their various views and concerns on the down-scheduling. In summary, it was submitted that on many occasions, pharmacists intervene in the inappropriate use of ibuprofen and other NSAIDs. Product label alone would not provide sufficient information to ensure safe use of ibuprofen, given its potential adverse effects and contraindications, and would not assist consumers in selecting a more suitable medication. XXXXXXXXXXX made the following recommendations: 1) to reschedule all products containing aspirin to

pharmacy/pharmacist only, and 2) to label all products containing paracetamol with the words “containing paracetamol” in font at least equal to the trade name of the pack.

ATTACHMENT 4 – SUMMARY AND TGA RESPONSE ON THE PUBLIC COMMENTS RECEIVED BY THE NDPSC FOLLOWING THE JUNE 2003 MEETING (PROVIDED BY MEC)- ITEM 13.7

GENERAL COMMENTS

Responses received	TGA Comment
XXXXXXXXXXX: Requested transition time of at least 12 months; XXXXXXXXXXX: Requested transition time of one year (in addition to the time it takes for the amendment to come into effect) to allow sponsors time to update labels, etc.	MEC recommended a 12 month transition time at its August meeting – MEC agreed at its October 2003 meeting that the transition time should be 12 months plus the time taken for the NDPSC amendment to come into effect.
XXXXXXXXXXX: The NDPSC must highlight that 'words to the effect' of the proposed warning statements will continue to be acceptable. Sponsors must be able to modify the statements to maximise their performance for consumers. XXXXXXXXXXX: Both the SUSDP and ARGOM allow *"words to that effect"* for warning statements.	The SUSDP already specifically advises that App F warning statements can be replaced by *"words to that effect"*.
XXXXXXXXXXX: Seeks consistent requirements, where appropriate, for all OTC analgesic products in order to minimise the risk of consumer confusion. Concerned that inconsistent labelling requirements may lead consumers to unnecessarily favour one analgesic over another.	The proposed warnings have been recommended by the MEC based on the properties of each analgesic. The statements differ in line with these properties.
XXXXXXXXXXX: Requested the NDPSC to consider applying the proposed paracetamol warning statements across all OTC analgesics if they are introduced (following satisfactory market testing).	See above.
XXXXXXXXXXX: Asked whether proposed statements are intended to replace current SUSDP App F warnings (34 and 35; and 71 for ibuprofen and naproxen).	The proposed statements are intended to replace all current SUSDP warnings.

Responses received	TGA Comment
XXXXXXXXXXX: Would appreciate clarification of how the guidance provided in ARGOM will operate once the new SUSDP statements are in place. XXXXXXXXXXX assume that the SUSDP statements will become mandatory as scheduling criteria, which will result in some statements included in ARGOM being repetitive.	The TGA will make any necessary changes to ARGOM to maintain consistency with the SUSDP App F warning statements. These changes will be made after the new SUSDP statements are implemented.
XXXXXXXXXXX: Requested the NDPSC to recognise *"that TGA approval of a label will be taken to denote compliance with the warning statements in the SUSDP and that the NDPSC confirms this in the minutes of its October meeting"*.	This is a matter for the NDPSC
XXXXXXXXXXX, XXXXXXXXXXX: Concerned about different interpretations by the States and Territories, NDPSC and MEC. Concerned that TGA approved-labels should be recognised as acceptable by States and Territories	This is a matter for the NDPSC
XXXXXXXXXXX: Warnings should be market tested before implementation to ensure their true intent will be met.	Sponsors are able to modify the SUSDP label warning statements provided the intent remains the same. Sponsors are encouraged to test their labels to ensure that most consumers can understand them. Under proposals being developed for 'consumer-focused labelling', guidelines are being developed to assist sponsors in doing this.

PARACETAMOL

Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor. *[Adults]*

Keep to the recommended dose. Do not take this medicine for longer than a 48 hours at a time unless advised to by a doctor. *[Children and adolescents]*

Responses received	TGA Comment
XXXXXXXXXXX: Industry concerned over the lack of precision in the proposed reference to *"for more than a few days at a time"*, but accepted that there is no better alternative at this stage.	Comment noted.
XXXXXXXXXXX: Considers that their current statement (on XXXXXXXXXXX Liquid), *"Do not exceed the recommended dose or use for more than 48 hours without seeking medical advice"* adequately meets the intention of the new recommendation, and is more restrictive and better promotes safe use. Proposed amendment of SUSDP statement to *"Do not exceed the recommended dose or use for more than 48 hours without seeking medical advice"*.	XXXXXXXXXXX statement is consistent with the meaning of the proposed statement and would therefore be accepted.

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.

Responses received	Comments
XXXXXXXXXXX: Agreed with the need for advice such as this, but concerned over practicality of its inclusion – its addition may decrease useability of the (XXXXXXXXXXX) labels and result in patient confusion or incorrect use.	Under 'consumer focused labelling', sponsors will be encouraged to review their labels to ensure that information can be found and understood by most consumers.

Responses received	Comments
XXXXXXXXXXX, XXXXXXXXXXX: Adoption of performance based labelling should be considered as a means of educating consumers about the appropriate and quality use of OTC analgesics before resorting to potentially alarmist warnings.	The MEC has advised that the additional warnings are necessary in the interests of public safety. 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.
XXXXXXXXXXX: Concerned that this statement, and rescheduling of ibuprofen (some packs would be unscheduled), may scare significant proportions of the population (who safely use paracetamol) and encourage increased, inappropriate use of other OTC analgesics.	The MEC has advised that the additional warnings are necessary in the interests of public safety. Paracetamol overdose can result in asymptomatic, delayed, potentially fatal liver damage. Overdoses with aspirin and other NSAIDs do not have these effects. Rescheduling of ibuprofen is a separate issue.
XXXXXXXXXXX: Concerned that use of the word 'overdose' on labels may encourage the use of paracetamol in suicides and/or deter people from using paracetamol, resulting in the use of less appropriate analgesics. XXXXXXXXXXX stated that, even if 'words to the effect' of these statements are acceptable, it is industry's experience that the TGA does, on occasion, insist on the use of the exact wording given in the App F statements in the SUSDP.	See above. The TGA will only agree to wording that is different to a SUSDP label warning statement where the words have the same intent as the SUSDP wording. This means that on some occasions a sponsor's proposal will not be accepted.
XXXXXXXXXXX: Proposed a requirement for overdose information, but without specifying any wording (to ensure that performance-based principles can be applied).	See above – also, as noted above, words with the same intent are currently accepted (which allows sponsors to apply performance-based principles).

Responses received	Comments
XXXXXXXXXXX, XXXXXXXXXXX: Concerned that including the PIC phone numbers would increase PIC workload substantially, and potentially generate fear in consumers.	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. MEC did not consider concerns over PIC workload to be a reason not to include this advice on labels, but suggested (Aug 2003) that the NDPSC Secretariat advise the XXXXXXXXXXX of the new warning statement, and request it be distributed to other PICs.
XXXXXXXXXXX: Considers that inclusion on labels of XXXXXXXXXXX toll-free phone number adequately addresses this issue, as they refer phone calls of concern to a healthcare professional or PIC.	This does not adequately address this issue. Not all paracetamol sponsors include toll-free phone numbers on labels; company medical information sections may not all be available 24 hours/day.
XXXXXXXXXXX: 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).	The proposed label statement has been recommended by the MEC. *"Serious"* is appropriate here, given that fatalities have occurred following liver damage from paracetamol overdose.

Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist

Responses received	TGA Comment
XXXXXXXXXXX: Agreed with the need for such advice, but concerned over practicality of its inclusion – its addition may decrease useability of the (XXXXXXXXXXX Liquid) labels and result in patient confusion or incorrect use.	Under 'consumer focused labelling', sponsors will be encouraged to review their labels to ensure that information can be found and understood by most consumers.

Other issues:

Responses received	TGA Comment
XXXXXXXXXXX: The NDPSC should consider applying the final proposed paracetamol warning statements across all OTC analgesics if they are introduced (following satisfactory market testing).	The proposed warnings have been recommended by the MEC based on the properties of each analgesic. The statements differ in line with these properties.

NSAIDS

1. **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*

2. 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.*

3. 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]

4. **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.*

COMMENTS:

Responses received	Comments
XXXXXXXXXXX, XXXXXXXXXXX: Concerned as to whether proposed statements are intended to replace current SUSDP App F warnings (34, 35 – and 71 for ibuprofen and naproxen).	Proposed statements are intended to replace current SUSDP warnings.
XXXXXXXXXXX: Duplication between requirements of SUSDP, ARGOM and TGAC for ibuprofen needs to be addressed.	There is a proposal to amend the *Therapeutic Goods Advertising Code* to remove the reference to labelling for analgesic warning statements in the Code. Any duplication in the ARGOM will be addressed after the SUSDP statements are implemented.

Responses received	Comments
XXXXXXXXXXX: The proposed statements do not cover all current ARGOM ibuprofen requirements. Stated that they understood that the TGA intended to change the current ARGOM statement, *"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"* to *"If you are receiving regular treatment with other medications, check with your pharmacist or doctor"*.	Any duplication in the ARGOM will be addressed after the SUSDP statements are implemented. Any proposal to change the ARGOM statement relating to drug interactions would need to be considered by the MEC. Drug interaction statements are usually not covered by the SUSDP so it is appropriate that they remain in the ARGOM. This allows flexibility in implementation for particular products.
XXXXXXXXXXX: Recommended amending App F warnings for ibuprofen as follows: 1. *Don't use [this product / name of the product] if you have a stomach ulcer.* Don't use … in the last 3 months of pregnancy. 2. *Don't use … if you are allergic to ibuprofen or anti-inflammatory medicines.* 3. *Unless a doctor has told you to, don't use … for more than a few days at a time;* 4. *Ask your doctor or pharmacist before use if you are receiving regular treatment with other medications.* 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. 5. *Unless a doctor has told you to, don't use … if you are pregnant.*	XXXXXXXXXXX proposed statements 1, 2, 3, 4 & 7 are consistent with (but more wordy than) proposed SUSDP statements, and would be acceptable. XXXXXXXXXXX proposed statement 6 is consistent with ARGOM requirements and was allowed on XXXXXXXXXXX XXXXXXXXXXX labels. It would be considered consistent with the proposed App F warning, *"Unless a doctor has told you to, don't use … if you have asthma"*. See above re XXXXXXXXXXX proposed statement 5.

Responses received	Comments
XXXXXXXXXXX: Concerns re equity across relevant non-prescription analgesics and other OTC medicines – queried why advice such as *"Do not take this medicine for longer than a 48 hours at a time unless advised to by a doctor"* was not also required on ibuprofen labels. XXXXXXXXXXX understood that it was required for paracetamol to address the risk of the analgesic/antipyretic masking more serious underlying conditions. XXXXXXXXXXX considers *"Unless a doctor has told you to, don't use … for more than a few days at a time"* does not adequately address this.	The proposed statements for adults for paracetamol and NSAIDs are practically identical. This statement for paracetamol in children is different (limited to 48 hours) because of concerns that continued use without medical advice may lead to liver damage in some cases. This is not an issue with ibuprofen.
XXXXXXXXXXX: Considered there is some overlap between the two warnings referring to pregnancy for aspirin, ibuprofen and naproxen, which may cause some consumer confusion (*"Don't use … in the last 3 months of pregnancy"* and *"Unless a doctor has told you to, don't use … if you are pregnant"*).	Both proposed warnings are appropriate. The former is a contraindication, the latter is a caution. The distinction may not be obvious to some consumers. However, the consumer will have the benefit of a doctor's advice if used in the first 6 months of pregnancy. The warning about not using in the last 3 months of pregnancy should be clear to all.

ATTACHMENT 5 - SUMMARY OF PUBLIC SUBMISSIONS FOR ORLISTAT - ITEM 14.1.1

- XXXXXXXXXXX supports the S3 scheduling of orlistat. The organisation has a current membership of over 34,000 persons with diabetes in XXXXXXXXXXX, the vast majority with Type 2 diabetes in which orlistat is able to lower cholesterol levels and improve glycaemic control. They consider that improvement of individual and community access to orlistat with its support programs will further enhance the outcome of quality education programs for diabetes.
- XXXXXXXXXXX support the rescheduling of orlistat from S4 to S3 for the following reasons:
  - Obesity is a major public health concern that is currently under-treated.
  - Orlistat is an effective treatment for this condition and is suitable for rescheduling to S3 due to its favourable safety profile.
  - Pharmacists are well equipped to safely and effectively administer orlistat in the S3 setting and are well placed to provide counselling and advice in the area of weight management.
- XXXXXXXXXXX supports the S3 scheduling, and believe that it will provide long term benefits to public health, reduced costs to the health system, and unproved health outlooks and general wellbeing.
- XXXXXXXXXXX supports the S3 scheduling of orlistat. XXXXXXXXXXX outlined that pharmacy has had to move towards incorporating Quality Use of Medicines (QUM) principles into its treatment of scheduled OTC products. Furthermore, he believed that the widespread adoption of the Quality Care Pharmacy Program (QCPP) and other protocols which support practice change are indicative of a very pro-active stance on the part of pharmacy organisations and individual pharmacies/pharmacists. It was highlighted that the institute, in co-operation with XXXXXXXXXXX, developed the "Weight Wise Program" (WWP) incorporating the Healthy Weight Management Standard, based on pharmacist's practice in the support of patients receiving orlistat on prescription. In his view, orlistat is a product which is capable of being handled appropriately and professionally by community pharmacies in Australia.
- XXXXXXXXXXX continues to support S3 scheduling of orlistat, and gives responses to a number of critical points addressed by the NDPSC in previous meetings.
  - Australia environment is ideal for first OTC experience of orlistat – OTC medicine supply with access to pharmacist assessment and advice in Australia is different from that in the US.
  - Pharmacists provide regular advice on the combination of lifestyle changes (controlled diet, regular exercise) and pharmacological intervention on weight control. Several different programs, the Pharmacy Self Care Program (PSCP), the

Weight Control Pharmacy Self Care Card (since 1998), Weight Wise Program (since February 2002), Your Weight Your Way (by the Terry White Chemists banner group) have been designed to assist consumers. Along with these programs, consumers need greater access to effective weight loss products.

- The pharmacy profession currently offers the community a sophisticated level of counselling capabilities on health issues. Currently 97.5% of pharmacists are registered for the Quality Care Pharmacy Program (QCPP), a program that is developed by XXXXXXXXXXX and adopted by community pharmacy and the private hospital pharmacy sector.
- The community pharmacy network is well placed to screen for conditions and potential adverse effects, and have the capabilities to assist a customer to identify and select an approach that will be effective for them.
- Pharmacist's assessment and counselling skills and daily communication with consumers allows them to appropriately assess those individuals for whom orlistat may be of benefit or risk, and prevent misuse.
- The orlistat Consumer Medicine Information provides an ideal opportunity to discuss the latest evidence regarding the need for fat soluble vitamin supplementation.

- XXXXXXXXXXX believes that orlistat has a good safety profile and meets the criteria for inclusion in S3. XXXXXXXXXXX considered that the availability of orlistat as a S3 medicine would enhance pharmacist's role to participate in public health intervention strategies for obesity management, and to further complement the role of medical practitioners and other health professionals. XXXXXXXXXXX does not support Appendix H listing or orlistat, since a good management plan is likely to require many aspects of self management which may or may not include treatment with orlistat.
- XXXXXXXXXXX and XXXXXXXXXXX supports the S3 scheduling of orlistat. They are Australia's largest pharmacy retail banner groups, with respectively 400 and 275 branded pharmacies Australia wide. They believe that they have demonstrated to be equipped with the essential knowledge and abilities to guarantee:
  - Appropriate use of orlistat in the community;
  - Appropriate safeguards to ensure the timely referral of at risk individuals to specialist care;
  - Monitoring of patient on-going use to ensure quality use of medicine guidelines are used for the patient's benefit.
- XXXXXXXXXXX does not support the S3 scheduling. The XXXXXXXXXXX consider that before a patient embarks on a course of treatment with orlistat, a full medical assessment is necessary, with particular reference to the possibility of diabetes. Additionally, more Australian experience should be accumulated with its

long-term use before its down scheduling, although orlistat appears to have a fairly benign side effect profile compared with most S4 drugs.

- XXXXXXXXXXX does not support the S3 scheduling of orlistat due to concerns over:
  - The preferred first-line treatment for obesity is non-pharmacologic therapies;
  - It may cause wrong public perception for early pharmacotherapy;
  - Potential misuse by people with eating disorders, and consequent vitamin deficiencies;
  - Unacceptable GI symptoms induced by orlistat combined with a high dietary fat intake.