Commonwealth Department of Health and Ageing

TGA THERAPEUTIC GOODS ADMINISTRATION

National Drugs and Poisons Schedule Committee

Record of the Reasons

37th Meeting
25-26 February 2003

The *Record of the Reasons* contains the basis of scheduling decisions and other outcomes arising from the meeting. Please note that the *Record of the Reasons* includes extracts from the NDPSC minutes which have been edited to remove confidential information.

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
ACSPA	Australian Chemicals Speciality 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
APVMA	Australian Pesticides and Veterinary Medicines Authority
ANZFA	Australia New Zealand Food Authority
APAC	Australian Pharmaceutical Advisory Council
APMA	Australian Pharmaceutical Manufacturers Association
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ARTG	Australian Register of Therapeutic Goods
ASCC	Australian Society of Cosmetic Chemists
ASCEPT	Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
BAN	British Approved Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee

CMI	Consumer Medicine Information
CNPMB	Chemicals and Non-Prescription Medicines Branch
COAG	Councils of Australian Governments
CPAS	Chemical Product Assessment Section
CPI	Consumer Product Information
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
EC	European Community
ECG	Electrocardiogram
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
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
GIT	Gastro-Intestinal Tract
GP	General Practitioner

GST	Goods and Services Tax
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
NRA	National Registration Authority for Agricultural and Veterinary Chemicals
NZ	New Zealand
OCS	Office of Chemical Safety
ODBT	Office of Devices, Blood and Tissues

OOS	Out of Session
OTC	Over the Counter
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
PMAA	Proprietary Medicines Association of Australia
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
TGAC	Technical Grade Active Constituent
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TOR	Terms of Reference
TSB	Toxic Substances Board
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

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

2.1 SUSDP, PART 1

There were no items for consideration.

2.2 SUSDP, PART 2

There were no items for consideration.

2.3 SUSDP, PART 3

2.3.1 ORGANOTIN COMPOUNDS

This item was deferred to a future meeting.

2.4.1 BORON TRIFLUORIDE, BIFLUORIDES AND HYDROSILICOFLUORIC ACID – APPENDIX F PART 3

PURPOSE

The Committee considered the Appendix F entries for boron trifluoride, bifluorides and hydrosilicofluoric acid to include Warning Statement (WS) 93 and to delete WS 91.

BACKGROUND

Corrosive fluorides were considered at the February 2002 meeting of the NDPSC. The Committee agreed to amend the Schedule entries for corrosive fluorides, including boron trifluoride, bifluorides and hydrosilicofluoric acid, which release or generate hydrofluoric acid to become more restrictive based on the entries for hydrofluoric acid. Amendments to Appendices E and F were also made.

The Appendix F WS 91 was listed in SUSDP No. 17 Amendment No. 1 in error. WS 91 concerns iodine and is not relevant to corrosive fluorides. The correct WS is WS 93 that states "causes severe burns, which are not likely to be immediately painful or visible".

DISCUSSION

The Committee noted that warning statement (WS) 91 had been included in error in SUSDP 17 Amendment No. 1 for boron trifluoride, bifluorides and hydrosilicofluoric acid. The Committee agreed to correct the Appendix F, Part 3 entry to read WS 93 in place of WS 91 to reflect the Committee's original intent.

DECISION 2003/37 - 1

The Committee agreed to amend the Appendix F entries for boron trifluoride, bifluorides and hydrosilicofluoric acid to include warning statement 93 and delete warning statement 91 to reflect the original intent of the Committee.

Appendix F, Part 3 – Amendment

Bifluorides – amend entry to read:

Bifluorides (including ammonium, potassium and potassium salts)

(a) when included in Schedule 5

Warning statement 2
Safety Directions 1,4

(b) when included in Schedule 6

Warning statements 1,17,93
Safety Directions 1,3,4,5,8,29,35

Boron Trifluoride – amend entry to read:

Boron Trifluoride (including mixtures that generate boron trifluoride)

(a) when included in Schedule 5

Warning statement 2
Safety Directions 1,4

(b) when included in Schedule 6 or 7

Warning statement 1,17,93
Safety Directions 1,3,4,5,8,29,35

Hydrosilicofluoric Acid – amend entry to read:

Hydrosilicofluoric Acid (including mixtures that generate hydrosilicofluoric acid)

(a) when included in Schedule 5

Warning statement 2
Safety Directions 1,4

(b) when included in Schedule 6 or 7

Warning statement 1,17,93
Safety Directions 1,3,4,5,8,29,35

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

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

3.1 FLUMIOXAZIN

PURPOSE

The Committee considered post-meeting comment received regarding the scheduling of flumioxazin at the October 2002 meeting.

BACKGROUND

The scheduling of flumioxazin was considered at the October 2002 meeting at which it was included in Schedule 7 and the Committee endorsed the use of WS 47 in the *Handbook of First Aid Instructions, Safety Directions and Warning Statements for Agricultural and Veterinary Chemicals* (FAISD) - " **WARNING - This product contains flumioxazin, which causes birth defects in certain laboratory animals. Women of childbearing age are advised not to mix, load or spray this product. They should keep out of crops being sprayed.**"

DISCUSSION

XXXXXXXXXX objected to the use of statement 47 above in combination with inclusion in Schedule 7, arguing that the issue of developmental toxicity may be more appropriately conveyed through the MSDS. This was based on the theoretical nature of the risk at the levels of exposure, lack of any similar requirement in the USA and parallels with bromoxynil, which also causes developmental toxicity in experimental animals.

(Paragraph deleted)

Members were advised by CPAS that warning statements indicate a potential (not hypothetical) hazard and those involved in the handling and use of a product should be made aware of the possibility of adverse effects. XXXXXXXXX recognised this need and will include a statement in the product MSDS. However, it is not certain that an MSDS will always be available to users of the product, whereas a relevant label statement

would ensure the appropriate communication of hazard. Further, it was not clear in what form the MSDS will provide "..an explanation of the risk.." in this case.

In relation to the perceived similarities with bromoxynil, CPAS advised that while bromoxynil treatment is associated with foetotoxicity in both rats and rabbits, the effects are mostly variations/anomalies and are only observed at doses, which are maternally toxic. Such minor fetal effects are commonly regarded as secondary to toxicity in the dams. Accordingly, it was CPAS' view that bromoxynil-containing products do not warrant a warning statement about the possibility of birth defects.

Members noted the information provided by CPAS and agreed that no new information had been provided to change the Committee's conclusions in relation to flumioxazin.

OUTCOME

The Committee confirmed the inclusion of flumioxazin in Schedule 7 on the basis of the following irreversible effects:

- Reproductive and developmental toxicity after both single oral and repeated oral and dermal dosing;
- Chronic hepatotoxicity following repeated dosing; and
- Induction of porphyria and the potential for photodermatitis;

The Committee also agreed that it remained appropriate to endorse the use of Warning Statement 47 - " **WARNING - This product contains flumioxazin, which causes birth defects in certain laboratory animals. Women of childbearing age are advised not to mix, load or spray this product. They should keep out of crops being sprayed.**" for flumioxazin in the *Handbook of First Aid Instructions, Safety Directions and Warning Statements for Agricultural and Veterinary Chemicals*.

3.2 CHLORINATING COMPOUNDS

PURPOSE

The Committee considered post-meeting comment on the scheduling of chlorinating compounds.

BACKGROUND

Chlorinating compounds were re-scheduled at the October 2002 meeting to come into effect in State and Territory legislation on 1 September 2003.

DISCUSSION

The XXXXXXXXX repeated their concern that the decision will promote the use of less effective unscheduled and lower scheduled products on the basis that these will be perceived as safer for not having the POISON label in their post-meeting comment.

The Committee noted that this issue had been previously raised by XXXXXXXXX and was dealt with in the discussion of the item at the October 2002 meeting.

The Committee also noted that Industry has been given adequate time to discuss labelling alternatives with the NRA, however there has been no proposals submitted to either the NRA nor the NDPSC.

DECISION 2003/37 - 2

The Committee reiterated its previous advice in relation to the use of the signal heading **POISON** for domestic products. While there may be a public perception of relative safety that would favour, irrespective of efficacy, the use of a Schedule 5 product labelled **CAUTION** over a Schedule 6 product labelled **POISON**, the Committee considered this was an educational issue that needed to be addressed by industry. The Committee agreed that this was still no justification for not properly labelling a poison and confirmed its initial decision **2002/36 - 4** from the October 2002 Meeting.

Schedule 5 – New Entry

DICHLOROISOCYANURIC ACID containing 40 per cent or less of available chlorine, **except** in:

(a) liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(b) liquid preparations containing less than 2 per cent of available chlorine; or

(c) other preparations containing 4 per cent or less of available chlorine.

Schedule 5 – Amendments

CHLORINATING COMPOUNDS – amend entry to read:

CHLORINATING COMPOUNDS containing 20 per cent or less of available chlorine, **except**:

(a) when separately specified in these Schedules;

(b) sodium hypochlorite;

(c) liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(d) liquid preparations containing less than 2 per cent of available chlorine; or

(e) other preparations containing 4 per cent or less of available chlorine.

CALCIUM HYPOCHLORITE – delete entry.

CHLORINATED LIME – delete entry.

DICHLOROISOCYANURATES – delete entry.

SODIUM HYPOCHLORITE – delete entry.

TRICHLOROISOCYANURIC ACID – delete entry.

Schedule 6 – Amendment

BROMOCHLORODIMETHYLHYDANTOIN – delete entry.

Schedule 6 – New entries

CHLORINATING COMPOUNDS **except**:

(a) when included in Schedule 5;

(b) when separately specified in these Schedules;

(c) sodium hypochlorite;

(d) in liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(e) in liquid preparations containing less than 2 per cent of available chlorine; or

(f) in other preparations containing 4 per cent or less of available chlorine.

DICHLOROISOCYANURIC ACID **except**:

(a) when included in Schedule 5;

(b) in liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(c) in liquid preparations containing less than 2 per cent of available chlorine; or

(d) in other preparations containing 4 per cent or less of available chlorine

Schedule 7 – Amendment

TRICHLOROISOCYANURIC ACID – delete entry.

3.3 EXTRACT OF LEMON EUCALYPTUS

PURPOSE

The Committee considered a post meeting comment in relation to the scheduling of extract of lemon eucalyptus.

BACKGROUND

The scheduling of extract of lemon eucalyptus was considered at the October 2002 meeting. The Committee agreed that on the basis of the acute toxicity in rats and eye irritancy in rabbits, extract of lemon eucalyptus be included in Schedule 5 with an exemption from the requirements of scheduling for preparations containing 40% or less of extract of lemon eucalyptus. The Committee also stated its opposition to the use of terms such as "natural" and "Safe on kids" where these may breach provisions of Part 1, Section 18 of the SUSDP.

DISCUSSION

XXXXXXXXX were pleased with the decision of the NDPSC and acknowledged that the term "Extract of Lemon Eucalyptus" has been adopted according to suggestions made by the NRA. However, XXXXXXXXX did express concern regarding the statement "safe for kids" and proposed the statement "OK for Kids 12 months and older" for consideration by the NRA. In regard to the term "natural", the NDPSC objections were noted and a modified statement along the lines" Repellent derived from natural lemon eucalyptus oil" would be put forward to the NRA.

The Committee noted that the proposed new statement "OK for Kids 12 months and older" had not been submitted to the NRA at the time of the meeting.

OUTCOME

The Committee agreed to confirm its initial scheduling decision from the October 2002 Meeting and refer the new statement to the NRA as these types of statements are a registration issue.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 VARIATION OF REQUIREMENT FOR CLAUSE 7(1)(D)

PURPOSE

The Committee considered an exemption from Part 2, Clause 7(1)(d) of the SUSDP for sodium dichloroisocyanurate.

BACKGROUND

The proposed exemption to the inclusion of "FIRE AND EXPLOSION HAZARD" in the signal heading and need for warning statement (WS) 23 "May cause fire or explosion", was initially reviewed by the NDPSC at the November 1999 Meeting. The Committee noted a number of difficulties with the submission. To allow further consideration, it was requested that the Company obtain a formal opinion on the oxidising potential from the Competent Authorities controlling the Australian Dangerous Goods (ADG) Code. The Company was also to provide data or reasoned argument to support each of the changes to warning statements and safety directions that it was seeking.

The Committee noted at the October 2002 meeting, the inclusion of supporting data in the form of chemical reports that appeared to demonstrate that the relevant products did not constitute a fire or explosion hazard. The applicant also stated that they had received a letter from the XXXXXXXXX agreeing that the product was not a "dangerous good" and was not required to carry a Class 5.1 Oxidising Agent diamond. The Committee noted however, that the letter from XXXXXXXXX had not been received. The Committee acknowledged that the proposal contained merit, but the Committee needed to be provided with a copy of the letter from XXXXXXXXX before the decision could be finalised.

DISCUSSION

The Committee noted from the field report by XXXXXXXXX that the product was not a class 5.1 "dangerous good" and hence a case had been established to allow for such products within the dichloroisocyanuric acid entries in the SUSDP.

Members also noted that there was a theoretical risk of separation in a solid formulation such as this, and that in consequence the suitability and robustness of the packaging were important in preventing egress or interaction with unphlegmatised oxidising agent (dichloroisocyanurates). Jurisdictional members advised that the existing packaging requirements for these substances would still apply, as the scheduling would not change, only the cautionary and warning statements would change.

Members agreed that the need or otherwise, for "fire and explosion" cautionary and warning statements on dichloroisocyanurates may be determined and certified by a relevant competent authority in Australia on a product by product basis based on the classification or not as a dangerous good class 5.1.

Members also noted that certain redundant entries in relation to chlorinating compounds remained in Appendices E and F. As these had no regulatory impact but may be a source of confusion in labelling chlorinating compounds, the Committee agreed to remove these entries.

The Committee noted the comments by XXXXXXXXX regarding the requirements for labelling inner packaging with transport warnings and agreed that the Secretariat investigate this matter further before bringing the issue back to a future meeting.

DECISION 2003/37 - 3

The Committee agreed that certain products containing dichloroisocyanurates, certified by a relevant competent Australian authority as not being a dangerous good of class 5.1, need not display the cautionary or warning statements in relation to causing fire or explosion. The Committee also agreed to remove redundant entries from Appendices E and F in relation to various chlorinating compounds.

Part 2, Paragraph 7(1)(d) - Amendment

Amend paragraph to read:

(d) if the poison is a dry chlorinating compound containing more than 10 per cent of available chlorine, **except** for preparations certified by a relevant State or Territory authority as not being a Dangerous Good of Class 5.1 (oxidising substances), with the cautionary statement –

FIRE AND EXPLOSION HAZARD

Appendix E - Amendments

Calcium hypochlorite - delete entry.
Chlorinated lime - delete entry.
Sodium hypochlorite - delete entry.
Sodium trichloroisocyanurate - delete entry.

Appendix F, Part 3 - Amendments

Bromochlorodimethylhydantoin - delete entry.

Dichloroisocyanurates - amend entry to read:

Dichloroisocyanurates	Warning Statements	Safety Directions
(a) in household cleaning or bleaching preparations.	20	
(b) in preparations containing less than 10 per cent of available chlorine.	11	1,4,10
(c) liquid preparations containing 10 per cent or more of available chlorine.	3,18	1,4,26,8,10, 19,17,18,20, 15,16,22,6
(d) dry preparations containing 10 per cent or more of available chlorine.	22,23,10,18	1,4,26,8,12,13, 14,19,17,18, 20,21,15,16,22
(e) dry preparations containing 10 per cent or more of available chlorine certified by a relevant State or Territory authority as not being a Dangerous Good of Class 5.1 (oxidising substances)	22,10,18	1,4,26,8,12,13, 14,19,17,18, 20,21,15,16,22
(f) in anti-bacterial tablets containing 2.5 g or less of sodium dichloroisocyanurate.	60	
(g) other compressed blocks or tablets containing 10 per cent or more of available chlorine **except** in preparations containing 21 g or less of sodium dichloro-isocyanurate for use in toilet cisterns only.	22,23,10	12,13,14,19, 17,18,21,15
(h) other compressed blocks or tablets containing 10 per cent or more of available chlorine certified by a relevant State or Territory authority as not being a Dangerous Good of	22,10	12,13,14,19, 17,18,21,15

Class 5.1 (oxidising substances) **except** in preparations containing 21 g or less of sodium dichloro-isocyanurate for use in toilet cisterns only.

4.2 APPENDIX B

PURPOSE

The Committee considered reinstatement of Appendix B into the SUSDP, consequential Amendments to the Introduction, Principles of Scheduling and Part 1 of the SUSDP.

BACKGROUND

The Committee agreed to a final draft of the proposed Appendix B at the October 2002 meeting. This outcome was gazetted and the draft included in the record of the reasons from the October 2002 meeting published on the NDPSC website for public comment.

DISCUSSION

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

- XXXXXXXXX strongly supporting the proposal and requesting that substances for which there are no products also be included in this list.

- XXXXXXXXX supporting the proposal.

Members noted that nisin had been included in the draft Appendix B and in view of the review of this substance under JETACAR Recommendation 6, it was not appropriate to include this antibiotic at this time.

The Committee also reconsidered information on sodium perborate from the May 2001 meeting.

OUTCOME

The Committee agreed that there was insufficient information to consider the scheduling of sodium perborate and agreed that it remain unscheduled.

DECISION 2003/37 - 4

The Committee agreed to reinstate Appendix B, a list of substances considered not to require control by scheduling, in the SUSDP.

Part 1 - Interpretation - Amendment

Sub-paragraph 2(g) - amend paragraph to read:

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

Principles of Scheduling - Amendment

Sixth paragraph - amend to read:

Substances in products which have been considered for scheduling but have been exempted from this standard may be listed in either Appendix A (general exemptions) or Appendix B (substances considered not to require control by scheduling).

Reading the Schedules - Amendment

Last paragraph - amend to read:

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

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

Appendix B – Amendment

Amend to read:

APPENDIX B

SUBSTANCES CONSIDERED NOT TO REQUIRE CONTROL BY SCHEDULING

[This appendix should be read in conjunction with Appendix A]

Appendix B – New entry after [This appendix should be read in conjunction with Appendix A]

INTRODUCTION

At various times, the NDPSC has considered substances for which the available information suggests that inclusion in the Poisons Schedules is not necessary or not the most appropriate means of controlling the risk to public health.

Listing in Appendix B indicates that a decision has been taken not to list substances anywhere in the Schedules, either for a specific purpose, or generally. It is an inclusive, but not an exhaustive, list ie. there may be substances not included in the Schedules, and not included in Appendix B, which may be hazardous or non-hazardous, but have not been considered in relation to the need for scheduling.

Substances may be included in Appendix B because they have intrinsically low toxicity, or where other factors suggest that the potential public health risk would be minimal. Factors which are considered when determining an Appendix B entry include:

- The toxicology profile was adequately characterised and not consistent with inclusion in any of the Schedules;
- The use, purpose or product presentation minimised any hazard to the public such as to not require scheduling; or
- The public access was limited such that scheduling was inappropriate or unnecessary.

The list has been developed from current scheduling files and historical records. For transparency, where the reason for entry and/or purpose or use for the substance was apparent in the consideration, this has been included in the columns “Reason for Entry” and “Area of Use”

Inclusion in Appendix B will not prevent reconsideration of the scheduling of a substance where adverse information becomes available about the Appendix B entry for that substance.

The NDPSC considers applications for scheduling. Applications for entry into Appendix B will not be accepted.

PART 1

REASONS FOR ENTRY

a Low Toxicity.

b Use pattern restricts hazard.

c Presentation/packaging restricts hazard.

d Industrial use only

PART 2

AREAS OF USE

1. Agricultural

1.1 Herbicide

1.2 Insecticide

1.2.1 Insecticide for codling moth

1.3 Fungicide

1.3.1 On seed fungicide

1.4 Bird Repellent

1.5 Fertiliser

1.6 Plant Growth Regulator

1.7 Insect Pheromone

1.8 Mushroom Bactericide

1.9 Acaricide

2. Veterinary

2.1 For animal use

2.2 Treatment of mastitis in cows

2.3 Coccidiostat

2.4 Feed additive

2.5 Antiseptic

2.6 Scabicide

2.7 Anthelmintic

2.8 Vitamin/Mineral

2.9 Growth Promotant

3. Domestic

3.1 Aromatherapy

3.2 Food additive

3.3 Cosmetic

3.4 Human use

3.5 Miticide

4. Industrial

4.1 Water Treatment

4.2 Biological control agent

5. Environmental

5.1 Mosquito control

6. Human therapeutic use

6.1 Diagnostic agent

6.2 Medical device

6.3 Antiseptic

6.4 Sunscreen

6.5 External Use

6.6 Laxative

6.7 Antiseborrheic

6.8 Cytoprotective

6.9 Vitamin/Mineral

6.10 Eye Drops

7. General

7.1 Any use.

7.2 Excipient

7.3 Synergist

7.4 Flux

7.5 Pesticide

7.6 Insect Repellent

7.7 Solvent

7.8 Disinfectant

7.9 Preservative

7.10 Antioxidant

7.11 Resin Activator/Accelerant

7.12 Sweetener Artificial

7.13 Food additive

PART 3

SUBSTANCES CONSIDERED NOT TO REQUIRE CONTROL BY SCHEDULING

As at February 2003

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
AGROBACTERIUM RADIOBACTER	Nov 1989	a	1
ALCOHOL, DEHYDRATED	Aug 2000	b	6
ALUM	May 1997	a	7.1
ALUMINIUM AMMONIUM SULFATE	May 1997	a	7.1
ALUMINIUM POTASSIUM SULFATE	May 1997	a	7.1
ALUMINIUM SILICATE	Nov 1974	a	7.1
ALUMINIUM tris (ETHYLPHOSPHONATE)	Aug 1986	a	1
AMINACRINE	Aug 1999	b	6.3
AMMONIUM PHOSPHATE	Nov 1974	a	7.1
AMMONIUM THIOSULPHATE	Nov 1974	a	7.1
AMPROLIUM	Jun 1969	a	2.3
AMYL ACETATE	Nov 1974	a	7.1
ASPARTIC ACID	-	a	6
ASULAM	May 1986	a	1
BACILLUS THURINGIENSIS (excluding endotoxin)	May 1992	a	5.1
BACILLUS TOYOI	Aug 1980	a	2.9
BACULOVIRUS CYDIA POMONELLA (Codling Moth Granulosis Virus)	Oct 2002	a	1.2.1
BENFLURALIN	-	a	1.1
BENSULFURON-METHYL	Aug 1987	a	1
BENTONITE	Jun 2002	a	7.1
BENZYL BENZOATE	Aug 1989	a	1,3.4
BETAINE HYDROCHLORIDE	Nov 1974	a	7.1
BIFENAZATE	Oct 2002	a	1.9
BISMUTH SUBNITRATE	Nov 1999	b, c	2.1
BIURET	Nov 1974	a	2.4
BOVINE SOMATOTROPHIN	May 1992	a	2
BROMACIL	Aug 1987	a	1
BROMOPROPYLATE	Nov 1994	a	1
BUPIRIMATE	Nov 1990	a	1
BUTAFENACIL	May 2000	a	1
BUTOXYPOLYPROPYLENE GYLCOL	Nov 1974	a	7.7

CARBETAMIDE	Aug 1991	a	1
CARBOXIN	Aug 1987	a	1
CARFENTRAZONE-ETHYL	Aug 1998	a	1
CETYL ALCOHOL	Nov 1974	a	7.1
CHAMOMILE OIL	Feb 2000	a	3.1
CHINA CLAY	Nov 1974	a	7.1
CHLORFLURENOL	Feb 1974	a	1.6
CHLORHEXIDINE	Nov 1974	a	7.8
CHLORIDAZON	May 1988	a	1
CHLOROXYLENOLS	Feb 1975	a	7.8
CITRONELLA OIL	Feb 2000	a	7.1
CLARY SAGE OIL	Feb 2000	a	7.1
CLOPIDOL	Nov 1974	d	2.3
COBALT NAPHTHENATE	-	d	7.1
COLOPHONY	Feb 1997	b	7.4
CROSPOVIDONE	Aug 1996	a	2
CULICINOMYCES CLAVOSPORUS	Nov 1982	a	5.1
CYCLAMIC ACID	Nov 1971	a	7.1
CYCLOHEXANE	Nov 1974	a	7.7
CYCLOHEXANOL ACETATE	-	a	7.7
CYROMAZINE	Nov 1980	a	2
DIAVERIDINE	Jun 1969	d	2.3
DICLAZURIL	Nov 2001	a	2.3
DIETHYL CARBONATE	-	a	7.1
DIFLUFENICAN	Feb 1987	a	1
DIKEGULAC-SODIUM	Mar 1980	a	1.6
DIMETHICONE		a	7.1
DIMETHYL ETHER	Nov 1988	d	4
d-PHENOTHRIN	Feb 1982	a	7.5, 1.2
DIPHENYLAMINE	Feb 1988	a	1
DIPROPYLENE GLYCOL MONOMETHYL ETHER	Nov 1987	a	4
DIURON	Nov 1987	a	1
DOCUSATE SODIUM (DIOCTYL SODIUM SULFOSUCCINATE)	Feb 1970	a	7.1
2,2-DPA	Nov 1989	a	1
EPSIPRANTEL	Nov 1991	a	2
ETHAMETSULFURON-METHYL	Nov 2000	a	1.1
ETHOPABATE	Jun 1969	d	2.3
ETHYL ACETATE	Nov 1974	a	7.1
ETHYL ALCOHOL	Nov 1974	a	7.1

ETHYLBUTYLACETYL-AMINOPROPRIONATE	Aug 2000	a	3.4
ETHYL BUTYRATE	-	a	7.1
ETHYL LACTATE	-	a	7.1
ETHYL METHACRYLATE	Nov 1974	a	7.1
FENFURAM	May 1977	a	1.3.1
FENHEXAMID	Feb 1999	a	1
FENOXYCARB	Feb 1988	a	1
FIR NEEDLE OIL (Canadian)	Feb 2000	a	7.1
FIR NEEDLE OIL (Siberian)	Feb 2000	a	7.1
FLUFENOXURON	Feb 1997	a	1
FLUMETSULAM	Feb 1992	a	1
FLUOMETURON	Aug 1989	a	1
FLUTOLANIL	Nov 2001	a	1.3
FLUROXYPYR	May 1986	a, c	1
FULLERS EARTH	Nov 1974	a	7.1
GERANIUM OIL	Feb 2000	a	7.1
GIBBERELLIC ACID	Nov 1974	a	1.6
HELIOTHIS NUCLEAR POLYHEDROSIS VIRUS	May 1981	a	1.2
HEXAFLURON	Nov 1988	a	1
HEXYL ACETATE	-	a	7.7
HEXYTHIAZOX	Feb 1988	a	1
HUMAN OSTEOGENIC PROTEIN-1 (OP-1)	Aug 2001	b	6.2
HYDROPRENE	Feb 1988	a	1
HYDROXYPROPYL CELLULOSE	Nov 1982	a	7.1
ICODEXTRIN	Nov 2000	b	6
INDOLE-3-ACETIC ACID	Feb 1985	b	1.6
ISOPRENE ALCOHOL	-	a	7.1
IPRODIONE	Feb 1997	a	1
ISOSTEARYL ALCOHOL ETHOXYLATE	Nov 1999	a	5.1
JUNIPER BERRY OIL	Feb 2000	a	7.1
KAOLIN	Nov 1974	a	7.1
KRESOXIM-METHYL	Aug 1999	a	1
KUNZEA OIL	Feb 2000	a	7.1
LAURYL ALCOHOL 91-DODECANOL)	Nov 1974	a	7.1
LAVANDIN OIL	Feb 2000	a	7.1
LAVENDER OIL	Feb 2000	a	7.1
LEAD, METALLIC	-	a	7.1
LEMONGRASS OIL	Feb 2000	a	7.1
LEPIDOPTEROUS SEX PHEROMONES	Nov 1990	a	1
LIMONENE (DIPENTENE)	June 2002	a	7.1

LINSEED FATTY ACIDS	Aug 1990	a	2.1
LINURON	Feb 1990	a	1
LIQUORICE, DEGLYCYRRHISINISED	May 1999	a	7.1
MALEIC HYDRAZIDE	Nov 1992	a	1
MANGANESE DIOXIDE	May 1999	b	1
MESOLSULFURON-METHYL	Feb 2002	a	1.1
METARHIZIUM ANISOPLIAE	Feb 2000	b	4.2
METHOPRENE	Aug 1987	a	1
METHOXYFENOZIDE	Nov 2000	a	1
METHYL ACETATE	-	a	7.7
METHYL BENZOQUATE	Nov 1974	d	2.3
METHYL p-HYDROXYBENZOATE	Nov 1974	a	7.9
METSULFURONMETHYL	Nov 1985	a	1.1
NAPROPAMIDE	Aug 1987	a	1
NAPTHYL ACETAMIDE	Nov 1974	a	1.6
n-BUTYL BUTYRATE	-	a	7.1
n-BUTYL LACTATE	-	a	7.1
NEROLI OIL	Feb 2000	a	7.1
NICABAZIN	Jun 1969	d	2.3
NORFLURAZON	Nov 1983	a	1.1
NOVALURON	Nov 2000	a	1
OCTYL ALCOHOLS	Nov 1974	a	7.1
ORANGE OIL, SWEET	Aug 2000	a	7.1
OXABETRINIL	Feb 1987	a	1
OXYFLUORFEN	May 2001	a	1
PALMAROSA OIL	Feb 2000	a	7.1
PATCHOULI OIL	Feb 2000	a	7.1
PENCYCURON	Aug 1994	a	1
PEPPERMINT OIL	Feb 2000	a	7.1
PHENMEDIPHAM	May 1989	a	1.1
PHYTASE	Feb 1996	a	2.4
PICLORAM	Aug 1987	a	1
PICOLINAFEN	May 2000	a	1
PINUS SYLVESTRIS (PINE NEEDLE) OIL	Feb 2000	a	7.1
PIPERONYL BUTOXIDE	Aug 1991	a	7.5
POLOXALENE	Nov 1974	a	7.1
POLYHEDROSIS VIRUS OF HELICO ZEA OCCLUSION BODIES	Nov 1996	a	1
POLY (GNRF) OVALBUMIN	Feb 1990	a	2
PORCINE SOMATOTROPHIN	Nov 1991	c	2
PROCYMIDONE	Feb 1991	a	1.3

PROPYLENE GLYCOL	Nov 1974	a	7.1
2-PROPYLENE GLYCOL 1-MONOMETHYL ETHER	Nov 1987	a	4
POLY DIALLYL DIMETHYL AMMONIUM CHLORIDE (PolyDADMAC)	Nov 1997	a	4.1
POLYSORBATE 20	May 2001	a	1
PROPAMIDINE	Nov 1992	d	6.10
PROPYL ACETATES	-	a	7.1
PSEUDOMONAS FLUORESCENS	May 1985	a	1.8
PYRIMETHANIL	Feb 1996	a	1
PYRIPROXYFEN	Aug 1994	a	1
QUASSIA	Nov 1974	d	6, 2.1
QUINOXYFEN	Nov 2001	a	1.3
ROSEMARY OIL	Feb 2000	a	7.1
SAGE OIL (Spanish)	Feb 2000	a	7.1
SANDALWOOD OIL	Feb 2000	a	7.1
SEAWEED & UNFRACTIONED SEAWEED EXTRACTS	Feb 1985	d	1.5
SIMAZINE	Nov 1987	a	1.1
SOMATOTROPIN, EQUINE	Feb 1997	b	2
SUCRALFATE	Aug 1982	a	6.8
SULESOMAB	Jun 2002	b	6.1
SULFOSULFURON	Feb 1998	a	1
SULPHATED POLYSACCHARIDES	-	a	7.1
TANNIC ACID	Dec 1965	a	7.1
TANNIC ACID/BENZYL ALCOHOL PRODUCT	Nov 1993	a	7.1
TERBACIL	Aug 1987	a	1
THAUMATIN	Nov 1990	a	3.2
THIDIAZURON	Nov 1989	a	1
TRIASULFURON	Feb 1988	a	1
TRICHODERMA HARZIANUM	May 1996	a	1
(Z)-9-TRICOSENE	Aug 1991	a	1
TRIETHYLENE GLYCOL	Nov 1974	a	7.1
TRIFLOXYSULFURON	Feb 2002	a	1.1
TRIFLURALIN	Aug 1990	a	1
TRIFORINE	Aug 1987	a	1
UREA	Nov 1974	a	7.1
^{13}C-UREA	May 2001	a	6.1
VETIVER OIL	Feb 2000	a	7.1
VINYL ETHER	Nov 1987	b	6
VITAMIN K	Jul 1963	a	6.9, 2.8

XANTHOPHYLL (, -CAROTENE-3,3'-DIOL; LUTEIN; VEGETABLE LUTEIN; VEGETABLE LUTEOL; BO-XAN)	Nov 1974	a	7.1
YLANG YLANG OIL	Feb 2000	a	7.1
ZINC NAPHTHENATE	-	a	1.3

4.3 LITHIUM IN PIGMENTS

PURPOSE

The Committee considered the scheduling of lithium when present as an excipient.

BACKGROUND

Lithium salts were included in Schedule 4 at the July 1967 meeting of NDPSC. The entry was amended at the February 1968 meeting to exempt preparations (eg Lithia Water) containing 0.01% lithium or less. An application for lithium in topical preparations was considered at the May 1985 meeting but lapsed due to lack of information. The entries were harmonised with New Zealand including an entry for dermal preparations (Schedule 2) over the period November 1998-November 2000.

Lithium is found naturally in a variety of minerals including tourmaline which may contain up to 2.5% lithium. The applicant requested that pigments (eg tourmaline) containing lithium be exempt from the requirements of scheduling. Dermal preparations containing lithium above 0.01% are included in Schedule 2 of the SUSDP.

At the June 2002 NDPSC meeting members supported, in-principle, a similar approach to that taken for iron oxides. This would exempt products from scheduling when present below a certain percentage as an excipient. However, the Committee agreed that further consultation was needed to establish an appropriate cut-off and to ensure that products with a therapeutically active or toxic concentration of lithium ion were not given an exempt status.

DISCUSSION

The Committee noted previous pre-meeting comment received from:

- XXXXXXXXX requesting that no change be made to the existing exemption for products containing 0.01% lithium or less.
- XXXXXXXXX requesting they be advised of the outcome.

The applicant provided information and argument in support of a 0.23% cut-off based on a theoretical lithium content for tourmaline of 2.3% and a maximum tourmaline content in dermal products of 10%.

Members noted that this information was consistent with data provided at the October 2003 meeting.

DECISION 2003/37 - 5

The Committee agreed to exempt products containing 0.25 % or less of lithium when present as an excipient.

Schedule 4 - Amendment

LITHIUM – amend entry to read:

LITHIUM (excluding when present as an excipient at 0.25 per cent or less of lithium) for therapeutic use, **except**:

(a) when included in Schedule 2; or

(b) in preparations containing 0.01 per cent or less of lithium.

Schedule 2 - Amendment

LITHIUM (excluding when present as an excipient at 0.25 per cent or less of lithium) in preparations for therapeutic dermal use containing 1 per cent or less of lithium **except** in preparations containing 0.01 per cent or less of lithium.

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

5.1 SUSDP, PART 4

There were no items considered.

5.2 SUSDP, PART 5

5.2.1 SODIUM HYDROXIDE

PURPOSE

The Committee considered the proposal to amend the sodium hydroxide and potassium hydroxide entries in Appendix F, Part 3 of the SUSDP, particularly in relation to the requirement for Safety Direction (SD) 28.

BACKGROUND

A proposal was been received from XXXXXXXXX seeking the removal of the Safety Direction 28 requirement for liquid preparations containing NaOH from Appendix F, Part 3 of the SUSDP. Safety Direction 28 "Do not mix with hot water" is required for preparations containing more than 0.5% of sodium hydroxide (NaOH) or potassium hydroxide (KOH).

DISCUSSION

The following points were raised by XXXXXXXXX in support of their proposal.

- Sodium and potassium hydroxide in the solid form will react violently with hot water because the dissolution is an exothermic process. Once these substances have been dissolved in water and cooled to ambient temperature, they do not react exothermically with water.
- To verify the claim, a test was conducted where a portion of different liquid caustic detergent products (containing 1-35% hydroxide) was added to boiling water. In all cases, there was no reaction other than dissolution of the detergent product and no increase in bubbling. Therefore, it is quite safe to add solutions of NaOH or KOH to hot water at virtually any concentration.
- The safety direction "Do not mix with hot water" is particularly problematic in the cleaning industry where liquid alkaline detergents are nearly always added to hot water by the cleaners who have done this safely for decades. Having this safety direction on the label will create queries and confusion in the cleaning industry. XXXXXXXXX liquid dishwashing detergent used in hospitals and restaurants around Australia contains over 18% sodium and potassium hydroxides dissolved in water (plus other cleaning agents) and is pumped into a dishwashing machine with a tank full of hot water at over 60°C. This is typical in the catering industry around the world.
- XXXXXXXXX suggested that Safety Direction 28 be required only for solid preparations containing more than 0.5% of sodium or potassium hydroxide, not for liquid preparations.

The evaluation report highlighted the following points:

- The submission stated that while the dissolution of solid hydroxides in water is exothermic, the dilutions of sodium hydroxide and potassium hydroxide solutions with water are not exothermic reactions, i.e. mixing the solutions does not generate heat. This latter statement is not correct. Dilution of concentrated solutions of sodium or potassium hydroxide is an exothermic reaction though much less so than for the solid.
- The heat of solution for various forms of sodium hydroxide to give a final solution of 15% NaOH at 25°C is as follows:

Solid flakes	1.08 kilojoules/gram NaOH
50% aqueous solution	0.52 kilojoules/gram NaOH
30% aqueous solution	0.13 kilojoules/gram NaOH

The heat of dilution falls off rapidly as the initial concentration of the NaOH solution decreases from 50% to 30%.

- While it appears to be common practice to add strongly alkaline liquid detergents to hot water, it is likely that the "hot water" is from a commercial water heater and has a temperature of less than 70°C. The concentration of sodium and potassium hydroxides in liquid detergents is unlikely to exceed 50% while most products are likely to be considerably less than 50%.
- The potential for splatter or spitting due to overheating when alkaline liquid detergents are added to water decreases with the water temperature and rate of addition to water. Increasing the stirring rate during addition of alkaline solution to water also decreases the risk of local overheating and splatter. On this basis, the potential risks from controlled addition of a solution containing 30% or less NaOH to water of equal volume or more, with stirring, is low.
- It was recommended that a new Safety Direction "when diluting, add to water at a controlled rate with agitation to avoid splattering", in place of Safety Direction 28 would provide an adequate safeguard against splattering for liquid detergents containing less than 30% sodium or potassium hydroxide.
- The proposed cut-off of 30% may represent a fairly conservative view and the Committee may wish to consider a higher concentration cut-off. Furthermore, for liquid preparations the lower level of 0.5% is very conservative and it is recommended that the Committee consider a level of 10% for exemption from SD28 without the alternative SD.
- The Safety Directions relating to gloves and eye protection should remain.
- No safety concerns are expected with regard to *automatic dispensing of alkaline detergent into a closed system dishwashing machines* which meet the relevant design specifications. Accordingly, it is proposed that products used solely for this purpose may be exempted from the requirement to have Safety Direction 28 on the label, although diversion of the product to manual uses may need to be considered.

The Committee agreed that dilution of commercial concentrations of liquid cleaning preparations containing alkali metal hydroxides would not boil or spit, even where hot water was used.

DECISION 2003/37 - 6

The Committee agreed to require Safety Direction (SD) 28 only for solid preparations containing greater than 0.5% of sodium or potassium hydroxide.

Appendix F, Part 3 – Amendment

Sodium hydroxide – amend entry to read:

Sodium hydroxide	Warning Statements	Safety Directions
(a) in preparations containing 0.5 per cent or less of sodium hydroxide.	5	1, 4, 6
(b) in solid preparations containing more than 0.5 per cent of sodium hydroxide.	2, 10, 78	3, 5, 28
(c) in liquid preparations containing more than 0.5% of sodium hydroxide	2, 10, 78	3, 5

Appendix F, Part 3 – Amendment

Potassium hydroxide – amend entry to read:

Potassium hydroxide	Warning Statements	Safety Directions
(a) in preparations containing 0.5 per cent or less of potassium hydroxide.	5	1, 4, 6
(b) in solid preparations containing more than 0.5 per cent of potassium hydroxide.	2, 10, 78	3, 5, 28
(c) in liquid preparations containing more than 0.5% of potassium hydroxide	2, 10, 78	3, 5

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

No items considered.

6. MATTERS REFERRED BY THE NATIONAL REGISTRATION AUTHORITY FOR AGRICULTURAL AND VETERINARY CHEMICALS

6.1 FENBUCONAZOLE

PURPOSE

The Committee considered the scheduling of fenbuconazole, a new fungicide.

BACKGROUND

XXXXXXXXX provided data in support of TGAC approval for fenbuconazole and registration of a new product XXXXXXXXX containing 240g/L fenbuconazole for use against a wide range of fungal diseases affecting fruits, vegetables, cereal crops, turf, ornamental plants and tree crops.

Fenbuconazole is a triazole fungicide and is claimed to have protectant, curative and eradicant properties. Fenbuconazole is similar to other triazole fungicides including isoconazole (S2, S3, S4, S6), diniconazole (S5), enilconazole (S5), hexaconazole (S5), propiconazole (S5, S6), azaconazole (S6), epoxiconazole (S2, S3, S4, S6), tebuconazole (S5), ketoconazole (S2, S4), miconazole (S2, S3, S4, S6), cyproconazole (S5), bitertanol (unscheduled) and econazole (S2, S3, S4, S6).

The mechanism of action of triazole fungicides, which include bitertanol, fluotrimazole and triazbutil, is by inhibition of sterol 14-α-demethylase, a microsomal cytochrome P450-dependent enzyme system. Triazoles impair the biosynthesis of ergosterol, leading to accumulation of 14-α-methylsterols, impairing the functions of certain membrane-bound enzyme systems such as ATPase, thus inhibiting the growth of fungi.

DISCUSSION

(Paragraphs deleted)

The Committee noted that as a class, the triazole fungicides all have the liver as the major target organ and show increased liver weights and liver toxicity in the acute and chronic trials. They are generally not mutagenic nor are they genotoxic.

The Committee noted that inclusion in Schedule 5 had been requested by the applicant and agreed that the data for the active constituent supported such an entry.

DECISION 2003/37 - 7

The Committee agreed that fenbuconazole be included in Schedule 5 of the SUSDP on the basis of reversible hepatotoxicity after repeat dosing and reproductive toxicity observed at high dose levels in rats.

Schedule 5 - New entry

FENBUCONAZOLE.

6.2 MORANTEL TARTRATE

PURPOSE

The Committee considered the scheduling of morantel tartrate.

BACKGROUND

Morantel tartrate is currently unscheduled and was previously (1972) included in Appendix B of the SUSDP (1972) on the basis of the low hazard associated with use of the product.

XXXXXXXXX provided data in support of approval for the registration of a new product XXXXXXXXX containing 167 g/kg of morantel tartrate (equivalent to 99 g/kg morantel) and 4 g/kg of abamectin for use as an oral paste to control worms, bots and skin lesions and microfilarae in horses. This product would currently be included in schedule 5 on the basis of the abamectin content.

Morantel tartrate is a tetrahydro-pyrimide anthelmintic similar in structure to pyrantel (currently S2 for human therapeutic use) and oxantel (oxantel embonate is currently S5 for the treatment of animals). Morantel is also available as a citrate salt and is registered for use as an anthelmintic in pigs, sheep, goats and horses.

DISCUSSION

(paragraphs deleted)

The Committee agreed that based on the acute toxicological profile, morantel should be included in Schedule 6 of the SUSDP with a cut-off to both Schedule 5 and exempt. The Committee noted that this was not expected to have any regulatory impact.

DECISION 2003/37 - 8

The Committee agreed that on the basis of the acute oral toxicity profile that morantel be included in Schedule 6 with a cut-off to Schedule 5 at 25% and a cut-off to exempt at 10%.

Schedule 6 – New entry

MORANTEL TARTRATE **except**:

(a) when included in Schedule 5;

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

Schedule 5 – New entry

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

OUTCOME

Additionally, the Committee agreed to foreshadow the inclusion of morantel in Schedule 6 and Schedule 5 of the SUSDP for consideration at the June 2003 meeting. The Committee recognised that all salts of morantel should be subject to the same scheduling control.

FORESHADOW

Schedule 6 – Amendment

MORANTEL TARTRATE – amend entry to read:

MORANTEL **except**:

(a) when included in Schedule 5;

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

Schedule 5 – Amendment

MORANTEL TARTRATE – amend to read:

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

6.3 BACILLUS SPHAERICUS STRAIN 2362

PURPOSE

The Committee considered the scheduling of *Bacillus sphaericus* strain 2362, a new active used as an anti-mosquito larvicide.

BACKGROUND

Bacillus sphaericus is a naturally occurring, spore-forming bacterium found in soil and aquatic environments. At the time of sporulation, *Bacillus sphaericus* produces a d-

endotoxin which is bound to the spores and is toxic to many species of mosquito larvae upon ingestion.

XXXXXXXXX have provided data in support of TGAC approval for a new active, *Bacillus sphaericus* strain 2362, and for a trial permit and registration of a new product XXXXXXXXX for use in the control of *Culex spp*., *Anopheles spp*., and *Aedes camptorhynchus*. It was proposed for use in a range of situations where mosquitoes breed, particularly in highly polluted water.

The production of XXXXXXXXX is a one-step process where the excipients are added to the fermentation slurry and dried to form the granulated end-use product.

DISCUSSION

(Paragraphs deleted)

The Committee noted that the storage directions for the product (store at 25°C) indicated the robustness of the organism.

DECISION 2003/37 - 9

The Committee agreed that on the basis of the low acute oral, dermal and inhalation toxicity and lack of mammalian pathogenicity that *Bacillus sphaericus* strain 2362 be exempt from scheduling and included in Appendix B for use as an anti-mosquito larvicide.

Appendix B Part 3 - New entry

BACILLUS SPHAERICUS STRAIN 2362.

Date: Feb 2003
Reason: a
Use: 5.1

6.4 CADUSAFOS

PURPOSE

The Committee considered the scheduling of encapsulated cadusafos.

BACKGROUND

Cadusafos is a phosphorodithioate organophosphate compound related to ethoprophos (S6, S7) and terbufos (S7). It is a broad-spectrum nematicide and insecticide used to control numerous soil pests. XXXXXXXXX is registered use in soil used to grow bananas, ginger, sugar cane and tobacco.

XXXXXXXXX provided data in support of registration of a new product XXXXXXXXX for use in the control of certain soil borne parasitic nematodes in turf. In this product, cadusafos is encapsulated in a polymer shell to limit the toxicity compared to the currently registered granular formulation XXXXXXXXX. The polymer shell releases cadusafos after several days once incorporated into the soil to provide the nematicidal effect. The exact mechanism of release is unclear.

DISCUSSION

(Paragraphs deleted)

The Committee noted that parathion-methyl (240 and 450 g/L CS), a similar encapsulated product, had be previously considered and was reviewed under the Existing Chemical Review Program (ECRP) in 1997. The Committee noted the following from the ECRP parathion-methyl review:

- The acute dermal toxicity for the CS products was very low under occlusion with the dermal LD_{50} in rats above 4000 mg/kg for the 450 CS.

- In comparative short-term repeat dose dermal studies (under occlusion) there was little difference in cholinesterase inhibition between the EC and CS preparations with NOEL for cholinesterase (ChE) inhibition about 11mg/kg bw/day in each case.

- While the above result was ascribed to drying of the CS product, minor differences in the protocols between the studies and low numbers of animals made interpretation difficult.

- An *in-vitro* absorption study in rats was also interpreted as drying of the beads and that subsequent release of parathion-methyl from the encapsulation beads may be a problem however problems with the protocol and lack of detail on the methodology made interpretation difficult.

The Committee acknowledged that these issues had been noted during discussion of the parathion-methyl products (Aug 1995, 1996 and May 1997) and although additional information had been requested in respect of storage stability and release on drying (on humans) this information had not been received. As a result, both the 240 and 450 CS parathion-methyl products were retained in Schedule 6 rather than rescheduled to Schedule 5.

In the absence of repeat dose short-term dermal toxicity studies for cadusafos, the Committee drew a comparison between the encapsulated parathion-methyl product and the encapsulated cadusafos product. The Committee noted that if the cadusafos is released on drying and subsequent rupture of the capsule, cadusafos may be present in the environment for 2-5 months depending on soil type. The Committee also noted that the potential dermal exposure may possibly be substantially greater than reported in the studies submitted in support of registration and that there was potential for significant

cholinesterase inhibition following repeated exposure to cadusafos residues from areas treated with cadusafos.

The Committee recognised that the use of an encapsulated product on sports fields provided an environment where regular users of the treated field may be exposed several times a week to cadusafos residues once rupture of the capsule has occurred. It was noted that if a sporting team trained and played match games on a field treated with this product, the exposure may be quite high, particularly for a contact sport. For a grounds-person working on a treated field, the exposure may be up to 8 hours per day, 5 days a week. Exposure could occur both by direct contact with soil and vegetation and via dust contamination. Members expressed general concern over potential sub-chronic exposure to cadusafos residue on playing field turf and requested the Secretariat to bring these concerns to the attention of the NRA.

The Committee understood that this product will be marketed in XXXXXXXXX packs and as such, its use could also extend to the home garden ie lawns. The Committee also noted that home garden use may have a potential exposure risk exceeding that of a sports field as children may play on the treated lawn every day for several hours. Members agreed that home garden use of cadusafos was not appropriate and requested the Secretariat to advise the NRA of the Committee's opinion.

The Committee agreed that the toxicity profile for the encapsulated product supported a Schedule 6 entry. However, based on the toxicity profile for the granular product, the Committee considered that continued inclusion of this product XXXXXXXXX in Schedule 7 remained appropriate.

Members noted that the effect of detergents on capsule stability had not been investigated and the effect of detergent and soaps in washing was unknown.

DECISION 2003/37 - 10

The Committee agreed that on the basis of the low acute oral, dermal and inhalation toxicity that encapsulated suspensions of cadusafos be included in Schedule 6 for preparations containing 20 per cent or less of cadusafos.

Schedule 7 – Amendment

CADUSAFOS – amend entry to read:

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

Schedule 6 – New Entry

CADUSAFOS in aqueous preparations containing 20 per cent or less of microencapsulated cadusafos.

6.5 MARBOFLOXACIN

PURPOSE

The Committee considered the scheduling of marbofloxacin.

BACKGROUND

Marbofloxacin belongs to the fluoroquinolone group of antibiotics that act through inhibition of the bacterial enzyme DNA gyrase. It is related to the veterinary antibiotics enrofloxacin (S4), difloxacin (S4) and orbifloxacin (S4) and a number of important human antibiotics including ciprofloxacin (S4) and ofloxacin (S4). The fluoroquinolones provide the treatment of last resort for Multiresistant *Staphlococcus aureus* (MRSA) and Vancomycin-Resistant Enterococci (VRE). The fluoroquinolone antibiotics can produce arthropathy both in immature humans and animals.

XXXXXXXXX provided data in support of TGAC approval for marbofloxacin and registration of a new product in four strengths XXXXXXXXX tablets containing 25mg, 50mg, 100mg and 200mg marbofloxacin respectively for use in the treatment of canine and feline skin, soft tissue infections and urinary tract infections (cystitis) in dogs.

DISCUSSION

(paragraphs deleted)

The Committee noted that including marbofloxacin in Schedule 4 would be consistent with the Government response to JETACAR. The Government response accepts the JETACAR proposal that all antibiotics for use in humans and animals be classified as S4 unless the relevant regulatory authorities and the NDPSC assess the substance as having low and acceptable risk of promoting antibiotic resistance and can be exempted from this scheduling class. The Secretariat advised that as marbofloxacin is used for companion animals only, it is not required to be assessed by EAGAR.

A member commented that as marbofloxacin was a member of the fluoroquinolone class of antibiotics, it should be used with caution in skeletally immature animals due to the potential to cause joint erosion. Further comment noted that the treating veterinarians would be able to use their discretion when treating young animals.

The Committee noted that the product was unlikely to be used in other animals other than those for which it was proposed (cats and dogs).

DECISION 2003/37 - 11

The Committee agreed to include marbofloxacin in Schedule 4 of the SUSDP on the basis of the need for professional diagnosis intervention and advice prior to its use, and

recommendations from JETACAR. Additionally, inclusion of marbofloxacin in Schedule 4 is consistent with the Government's response to Recommendation 6.

Schedule 4 – New Entry

MARBOFLOXACIN.

6.6 IVERMECTIN

PURPOSE

The Committee considered the scheduling of a new ivermectin product for use in cattle.

BACKGROUND

Ivermectin was first scheduled in 1980. Over the subsequent years there has been a number of considerations relating to the use of ivermectin in cattle. Preparations containing 1% or less of ivermectin for the treatment of cattle, when supplied in sealed containers for use in automatic injection equipment were included in Schedule 6 at the November 1989 meeting. The Committee considered new information concerning the use of ivermectin as a pour on cattle product containing 5mg/mL ivermectin and as a jetting fluid containing 75mg/mL ivermectin at the August 1992 meeting of the NDPSC. Based on the low dermal absorption of the pour-on product, preparations containing 0.5% or less of ivermectin for dermal application to cattle were included in Schedule 6. As the acute oral toxicity for the jetting fluid was high at 75mg/mL, the Committee agreed that the jetting fluid should remain in Schedule 7.

The Committee reviewed the Schedule 6 entry for ivermectin at the February 1996 meeting of the NDPSC and amended the Schedule 5 entry to include internal use for the treatment of animals at 2% or less except when in Schedule 4, amended the Schedule 6 entry to include external use for the treatment of animals at 2% or less and amended the Schedule 7 entry to include all other uses which were not covered by Schedules 4, 5 or 6. The Committee considered both the Schedule 5 and the Schedule 6 entries at the August 1996 meeting of the NDPSC and agreed to delete the Schedule 6 entry and include preparations containing 2% or less and intraruminal implants containing 160mg or less of ivermectin in Schedule 5. The Schedule 7 entry was adjusted accordingly.

DISCUSSION

(Paragraphs deleted)

The Committee, while noting that the evaluator considered the new ivermectin product could be included in Schedule 5 based on the proposed use pattern and packaging, expressed concern over the potential risk of accidental poisoning in children.

The Committee agreed that if the product was packaged with a child-resistant closure, the concerns over accidental poisoning in children would be allayed.

DECISION 2003/37 - 12

The Committee agreed that on the basis of the proposed use and packaging, the Schedule 5 entry for ivermectin be amended to include formulations containing 3.5% or less of ivermectin when packed in a container fitted with a child-resistant closure.

Schedule 5 – Amendment

IVERMECTIN – amend entry to read:

IVERMECTIN for use in animals:

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

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

(c) in preparations containing 3.5 per cent or less of ivermectin when packed in a container fitted with a child-resistant closure; or

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

7. MATTERS REFERRED BY SCIENTIFIC DIRECTOR OF THE NON-PRESCRIPTION MEDICINES BRANCH

There were no items considered.

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 National Registration Authority (NRA), 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 that the scheduling of growth promoters/others scheduled outside S4 with no NRA registrations outside of S4 would be reviewed at the February 2003 meeting. This intention was included in the post- June 2002 meeting notice published in the Commonwealth of Australia Gazette No GN 32, 14 August 2002.

The Committee also agreed that the scheduling of virginiamycin would be reviewed at the February 2003 meeting after the final report form the NRA was received. This intention was included in the pre - February 2003 meeting notice published in the Commonwealth of Australia Gazette No GN 01, 8 January 2003.

The Committee agreed to consider each substance gazetted for consideration at the February 2003 meeting individually. These were: viginiamycin (8.1), bacitracin (8.2), cuprimyxin (8.3), erythromycin (8.4), hygromycin (8.5), naladixic acid (8.6), nisin (8.7), spiramycin (8.8) and avoparcin (8.9).

8.1 VIRGINIAMYCIN

PURPOSE

The Committee considered the scheduling of virginiamycin.

BACKGROUND

Virginiamycin was first scheduled prior to 1969. Virginiamycin is a streptogramin antibiotic used for the treatment of infections due to sensitive organisms, particularly gram positive bacteria. It is registered for use in cattle, sheep, horses, pigs and poultry as prophylaxis against lactic acidosis and/or as a growth promotor.

Virginiamycin was the only animal agent in the streptogramin class. There is only one product of this class for human use available in Australia – quinupristin-dalfoprisitin (QD, brand name XXXXXXXXX) which is indicated for use in the treatment of suspected or proven methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus faecium* infections requiring intravenous therapy where other antibiotics are inappropriate.

DISCUSSION

Two submissions have been received from XXXXXXXXX (June 2002 and February 2003). The company requested that the use in cattle be separated from the use in pigs and poultry when the Committee considered the scheduling of virginiamycin. XXXXXXXXX argued that ruminants, such as adult cattle and wool producing sheep, pose a negligible source of resistant organisms to humans. XXXXXXXXX highlighted that cattle and sheep farmers in remote regions may be poorly serviced by veterinarians and as such, may be denied access to virginiamycin products. These products are vital to preserve both animal welfare and animal life, particularly during drought feeding, but also when grain supplementation is required due to seasonally marginal pasture conditions.

The Committee noted in the Expert Advisory Group on Antimicrobial Resistance (EAGAR) report that

- *In vitro* studies confirm that virginiamycin resistance results in complete cross-resistance to pristinamycin (oral antibiotic available in France) and QD. Selection for resistance to virginiamycin in staphylococci and streptococci generally confers resistance to all macrolides and lincosamines. Macrolides (eg. erythromycin, roxithromycin, azithromycin and clarithromycin) are widely used in human medicine for a broad range of indications. The lincosamines (eg. lincomycin and clindamycin) are used less frequently. Selection of resistance to virginiamycin in *E. faecium* usually does not confer resistance to other classes. However, in theory, virginiamycin is capable of perpetuating vancomycin-resistant *E. faecium* in animal populations.

- It is possible for virginiamycin resistance to be selected in a wide range of intestinal Gram-positive bacteria. The most important organisms likely to be affected are those in which multi-antibiotic-resistance may already be present, especially vancomycin-resistant *E. faecium*. Selection of virginiamycin resistance in vancomycin-resistant *E. faecium* and transmission of such strains through the food chain could represent a significant hazard to humans.

- One German study reported that no QD resistant enterococci were isolated on the farms not using virginiamycin. All manure samples from farms using virginiamycin yielded QD resistant *E. faecium*.

- It is likely that virginiamycin-resistant *E. faecium* will spread to humans via the food chain. It is not known whether the resistance is spread through colonisation of humans with animal strains, or via the transfer of resistance genes from animal to human enterococci in the human gut.

- EAGAR recommended that virginiamycin be included in Schedule 4 of the SUSDP for all species, including cattle based on the fact that younger animals and some older cattle may carry *E.faecium*. Segregation of younger and older cattle is not always possible, and therefore exposure of calves to in-feed virginiamycin may occur with some frequency.

Pre-meeting correspondence was received from- XXXXXXXXX. XXXXXXXXX objected to the restriction of virginiamycin products for use in cattle and sheep on the basis that it can be a very valuable product in times of drought such as those being currently experienced. Virginiamycin is added to high-grain rations for between one and two weeks to prevent the development in those animals of lactic acid poisoning following too-rapid ingestion of grain in high feed concentrations. If virginiamycin was included in Schedule 4, this could result in animal welfare being compromised as many farmers do not have adequate access to veterinary surgeons from whom they would need authority to purchase these products. XXXXXXXXX proposed two alternate scheduling options that would accommodate this use in cattle and sheep for the treatment of feed-related acidosis.

The NRA advised virginiamycin was not the only treatment available for feed-related acidosis. Other substances including some ionophores may also be used for the treatment for acidosis and are currently included in Schedule 5.

Another member noted that virginiamycin is restricted in its use in New Zealand. It can be used when the organism is susceptible only to virginiamycin and to no other agent. Members noted that the inclusion of all uses of virginiamycin in Schedule 4 would result in harmonisation with New Zealand.

DECISION 2003/37 - 13

The Committee agreed to include virginiamycin for all uses in Schedule 4 of the SUSDP on the basis that continued unrestricted use poses an unacceptable risk to human health from the development and transfer of organisms resistant to this class of antibiotics in food animals. Additionally, inclusion of virginiamycin in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6 and advice received from EAGAR.

Schedule 4 - Amendment

VIRGINIAMYCIN – amend entry to read:

VIRGINIAMYCIN.

Schedule 5 – Amendment

VIRGINIAMYCIN – delete entry.

8.2 BACITRACIN

PURPOSE

The Committee considered the scheduling of bacitracin.

BACKGROUND

Bacitracin is classed as a polypeptide antibiotic. It is used as a feed premix as a growth promotant and as a treatment for necrotic enteritis in poultry. It is widely used for the treatment of eye and ear infections and skin infections in animals generally.

Bacitracin was first scheduled prior to 1968 under the generic entry for antibiotics. Bacitracin was included as an individual entry in Schedule 4 at the May 1978 meeting. The scheduling of this substance has been reviewed periodically, and has essentially remained unchanged since its initial inclusion in the standard.

DISCUSSION

A pre-meeting submission was received from XXXXXXXXX. The submission concluded that bacitracin poses a negligible threat in regard to antibiotic resistance and as such, XXXXXXXXX requested no changes to the current scheduling of bacitracin.

The Expert Advisory Group on Antimicrobial Resistance (EAGAR) provided a scheduling assessment which recommended that all uses of bacitracin be scheduled as S4. EAGAR believed that scheduling outside of S4 would pose an unacceptable risk of promoting antimicrobial resistance as continued non-prescription (unregulated) use will raise the likelihood of escalating resistance when used therapeutically in animals. Experimental evidence linking bacitracin to vancomycin resistance is equivocal. Bacitracin is listed by JETACAR as a category A antibiotic (essential antibiotics for treatment or prevention of animal infections where there are few or no alternatives for many infections) for meat chickens and layer hens for prevention of necrotic enteritis. While there are human uses for bacitracin, it is not considered to be an important antibiotic and a reasonable number of alternative agents in different classes are available to treat these infections.

The EAGAR concluded that the continued use of bacitracin as a growth promotant could compromise its effectiveness as a treatment of necrotic enteritis in poultry.

The Committee noted the EAGAR had reviewed and considered the pre-meeting submission from XXXXXXXXX when recommending bacitracin be included in S4 for all uses.

DECISION 2003/37 - 14

The Committee agreed to include bacitracin for all uses in Schedule 4 of the SUSDP on the basis that use outside of S4 poses an unacceptable risk of promoting antimicrobial resistance and would raise the likelihood of escalating resistance when used therapeutically in animals. Additionally, inclusion of bacitracin in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6 and advice received from EAGAR.

Schedule 4 – Amendment

BACITRACIN – amend entry to read

BACITRACIN.

Schedule 6 – Amendment

BACITRACIN – delete entry.

8.3 CUPRIMYXIN

PURPOSE

The Committee considered the scheduling of cuprimyxin.

BACKGROUND

Cuprimyxin is a broad-spectrum antibacterial and antifungal agent. It was used for the topical treatment of superficial infections in horses, dogs, and cats caused by bacteria, dermatophytes and yeast affecting the skin, hair, and external mucosae.

The Committee first considered cuprimyxin in May 1977 and it was included in Schedule 5 of the SUSDP.

DISCUSSION

It was outlined that the Expert Advisory Group on Antimicrobial Resistance (EAGAR) recommended the removal of the S5 cuprimyxin entry as there are currently no registered products containing cuprimyxin. EAGAR indicated it would consider cuprimyxin should a product be submitted for registration.

The Committee noted that the exclusion of cuprimyxin from the SUSDP would remove regulatory controls currently in place. The inclusion of cuprimyxin into Schedule 4 of the SUSDP would provide a further measure of control for the personal importation of therapeutic goods under the Therapeutic Goods legislation. A written authority issued by a medical practitioner registered under a law of a State or Territory is required for Schedule 4 substances, except where the goods are carried by the importer as a passenger on a ship or aeroplane.

DECISION 2003/37 - 15

The Committee agreed to include cuprimyxin for all uses in Schedule 4 of the SUSDP on the basis of EAGAR's recommendation. Additionally, it was noted that inclusion of cuprimyxin in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6.

Schedule 5 - Amendment

CUPRIMYXIN – delete entry.

Schedule 4 – New entry

CUPRIMYXIN.

8.4 ERYTHROMYCIN

PURPOSE

The Committee considered the scheduling of erythromycin.

BACKGROUND

Erythromycin was first scheduled prior to 1968. Erythromycin is a macrolide antibiotic with a wide spectrum of activity that is used in the treatment of a wide variety of infections in cattle, sheep and poultry.

DISCUSSION

The Expert Advisory Group on Antimicrobial Resistance (EAGAR) provided an assessment of erythromycin. The Committee noted that while the human importance of erythromycin is low, it is generally regarded as a second to third line agent for many human infections caused by susceptible microorganisms. Increasing resistance will further reduce the utility of macrolides, but alternatives exist. Accordingly, EAGAR recommended that all uses of erythromycin be scheduled as S4. The rationale for this recommendation was as follows:

It poses an unacceptable resistance risk outside Schedule 4 because:

- Erythromycin resistance can be generated in animals and spread to humans, adding to the macrolide resistance burden in both groups.

- It can encourage co-selection of resistance to unrelated classes of antibiotics, and sometimes to classes with the same mechanism of action such as the lincosamides and streptogramins B.

- It is an important therapeutic agent in some animal species (the JETACAR rating for animals is high for some species).

DECISION 2003/37 - 16

The Committee agreed to include erythromycin for all uses in Schedule 4 of the SUSDP on the basis of EAGAR's recommendation that use outside of S4 poses an unacceptable

risk of promoting antimicrobial resistance and the transfer of this resistance from animals to humans. Additionally, inclusion of erythromycin in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6.

Schedule 4 – Amendment

ERYTHROMYCIN – amend entry to read:

ERYTHROMYCIN.

Schedule 6 – Amendment

ERYTHROMYCIN – delete entry.

8.5 HYGROMYCIN

PURPOSE

The Committee considered the scheduling of hygromycin.

BACKGROUND

Hygromycin was first scheduled in 1968 and included in Schedule 4 of the SUSDP. Hygromycin B is an aminoglycoside antibiotic that inhibits protein synthesis in bacteria and fungi. It was used as an anthelmintic in veterinary medicine for the treatment of nematode infections.

DISCUSSION

The Expert Advisory Group on Antimicrobial Resistance (EAGAR) had provided the Committee with interim advice that all uses as hygromycin be included in S4 as this anitmicrobial selects for cross-resistance to aminoglycosides of human importance.

DECISION 2003/37 - 17

The Committee agreed to include hygromycin for all uses in Schedule 4 of the SUSDP on the basis of EAGAR's recommendation that use outside of S4 poses an unacceptable risk of promoting cross resistance to aminoglycosides of human importance. Additionally, the inclusion of hygromycin in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6.

Schedule 4 – Amendment

HYGROMYCIN – amend to read:

HYGROMYCIN.

Schedule 6 – Amendment

HYGROMYCIN – delete entry.

8.6 NALIDIXIC ACID

PURPOSE

The Committee considered the scheduling of nalidixic acid.

BACKGROUND

Nalidixic acid is a 4-quinolone antibacterial used in the treatment of uncomplicated lower urinary tract infections due to Gram-negative bacteria other than Pseudomonas spp. It has also been used to treat shigellosis.

The Committee first considered nalidixic acid at the July 1965 meeting and it was included in Schedule 4 of the SUSDP. Nalidixic acid was reviewed again at the November 1985 meeting and the Committee included a new Schedule 6 entry for this substance when packed and labelled for the treatment of ornamental fish.

DISCUSSION

The Expert Advisory Group on Antimicrobial Resistance (EAGAR) provided the Committee with interim advice that all uses of naladixic acid be included in S4 as this therapeutic class is important in human medicine.

DECISION 2003/37 - 18

The Committee agreed to include nalidixic acid for all uses in Schedule 4 of the SUSDP on the basis that it belongs to a therapeutic class which is important in human medicine. Additionally, inclusion of nalidixic acid in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6.

Schedule 4 – Amendment

NALIDIXIC ACID – amend entry to read

NALIDIXIC ACID.

Schedule 6 – Amendment

NALIDIXIC ACID – delete entry.

8.7 NISIN

PURPOSE

The Committee considered the scheduling of nisin.

BACKGROUND

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

The May 1978 Meeting agreed to exclude nisin, which was considered exempt from scheduling at the time, from the generic entry for 'antibiotics' in Schedule 4. In November 1998, the NZ MCC agreed to adopt the S4 generic statement for antibiotic substances but did not adopt the exemption for nisin although no reason was stated in the MCC Minutes.

DISCUSSION

The Expert Advisory Group of Antimicrobial Resistance (EAGAR) Secretariat has advised that there are no resistance issues associated with nisin as this is a class that has no human analogues or cross resistance issues. However, a recent study published under the auspices of the United States Department of Agriculture, Agriculture Research Service (ARS), has reported that the ruminal bacterium, *Streptococcus bovis*, could develop nisin resistance after only a short period of exposure. This was stated to be due to an alteration in lipoteichoic acids, and this change also caused an increase in ampicillin resistance (Applied and Environmental Microbiology, February 2001).

OUTCOME

The Committee agreed that the unscheduled status of nisin remains appropriate and to reconsider the matter following receipt of the EAGAR assessment.

8.8 SPIRAMYCIN

PURPOSE

The Committee considered the scheduling of spiramycin.

BACKGROUND

Spiramycin was first scheduled prior to 1978. Spiramycin is a macrolide antibiotic that has been used similarly to erythromycin in the treatment of susceptible bacterial infections. It has also been used in the protozoal infections, cryptosporidiosis and toxoplasmosis.

DISCUSSION

The Expert Advisory Group on Antimicrobial Resistance (EAGAR) provided an assessment which recommended that all uses of spiramycin be scheduled as S4. The rationale for this recommendation was as follows:

Scheduling outside S4 would pose an unacceptable risk of promoting antimicrobial resistance because of:

- Known resistance problems in similar 16-membered macrolides in animals; and
- Its capacity to co-select for resistance in 14-, 15- and 16-membered macrolide, lincosamide and streptogramin B antimicrobials.

DECISION 2003/37 - 19

The Committee agreed to include spiramycin for all uses in Schedule 4 of the SUSDP on the basis of EAGAR's recommendation that use outside of S4 poses an unacceptable risk of promoting antimicrobial resistance. Additionally, inclusion of spiramycin in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6.

Schedule 4 – Amendment

SPIRAMYCIN – amend entry to read:

SPIRAMYCIN.

Schedule 6 – Amendment

SPIRAMYCIN – delete entry.

8.9 AVOPARCIN

PURPOSE

The Committee considered the scheduling of avoparcin.

BACKGROUND

Avoparcin is a glycopeptide antibiotic that has been incorporated into animal feedstuffs to promote growth.

The Committee first considered avoparcin in 1976 and it was included in Schedule 4 of the SUSDP. Subsequently at the February 1990 meeting the Committee amended the entry to also exempt animal feeds as intended. In the late 1990's the NRA initiated a review of avoparcin which was suspended when the registrants withdrew the product from the market. Registration and approval ceased on the 30 June 2000.

DISCUSSION

The Expert Advisory Group on Antimicrobial Resistance (EAGAR) assessed avoparcin and recommended that it could be removed from the SUSDP as the product had been withdrawn worldwide and was no longer registered in Australia. If the NDPSC wanted to continue the scheduling of this antibiotic, EAGAR recommended it be scheduled as S4 as its selection for resistance to antibiotics in humans is of high importance (vancomycin).

The Committee noted that the removal of avoparcin from S4 would permit personal importation and use without control.

DECISION 2003/37 - 20

The Committee agreed to include avoparcin for all uses in Schedule 4 of the SUSDP on the basis that use outside of S4 poses an unacceptable risk of promoting resistance to antibiotics of high human importance (vancomycin). Additionally, inclusion of avoparcin in Schedule 4 of the SUSDP would be consistent with the Government response to JETACAR Recommendation 6.

Schedule 4 – Amendments

AVOPARCIN – amend entry to read:

AVOPARCIN.

9. OTHER MATTERS FOR CONSIDERATION

There were no items considered.

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

There were no items considered.

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

There were no items considered.

PHARMACEUTICALS

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

12.1 AZADIRACHTA INDICA (NEEM)

PURPOSE

The Committee considered the post-meeting comments received in relation to the October 2002 decision to schedule *Azadirachta indica* (neem).

BACKGROUND

The October 2002 NDPSC Meeting considered the scheduling of *Azadirachta indica* (neem), following an initial review of data and related literature at the February 2002 meeting. At the October 2002 meeting, the Committee remained concerned over the potential toxicological hazards from oral and dermal exposure to neem and its extracts and derivatives. The evidence reviewed by the Committee included reports of serious poisonings in children and embryotoxic, abortifacient and antiandrogenic effects in laboratory animals. On these grounds, the Committee agreed that the availability and presentation of certain neem products for sale to the public warranted restrictions in order to protect public health and safety. Hence, the Committee recommended that preparations containing neem or its extracts or its derivatives for human internal use be prohibited in Australia, except those containing 'debitterised' neem seed oil. 'Debitterised' neem seed oil was excluded from scheduling action as it was not of toxicological concern. The Committee however agreed that some neem products could remain available for sale to the public provided they are appropriately labelled and packaged.

DISCUSSION

The Committee noted the following points raised in the October 2002 post-meeting submissions:

- XXXXXXXXX acknowledged the decision to schedule *Azadirachta Indica* derivatives in Schedule 6 with several exemptions but also raised the following points:
    - The exemption should include cold pressed neem seed oil for agricultural use at an on farm dilution containing 0.5% or less of cold pressed neem seed oil.
    - Neem seed oil was preferred to alcoholic or aqueous neem extracts in terms of efficacy in agricultural use and was a safer alternative to poisonous chemicals.
    - Based on available evidence, cold pressed neem seed oil should be exempt from scheduling and a maximum allowable aflatoxin level be established.

(Secretariat Note: The proposals to also exempt from scheduling 0.5%-1% cold-pressed neem seed oil for use in agriculture appeared to be based on the end-use or 'on farm' final dilution of a concentrated product containing cold pressed neem seed oil.)

- XXXXXXXXX first submission, on behalf of XXXXXXXXX, stated that whilst they agreed with much of the Committee's findings, the proposed scheduling of cold pressed neem oil as a Schedule 6 poison was not supported. This assertion was made on the basis that they believed there was sufficient evidence to warrant inclusion of cold-pressed neem seed oil in Schedule 5. In addition, it was argued that the appropriate exemption level for preparations for human dermal use containing cold pressed neem oil should be 2% at minimum, not 1%.
- XXXXXXXXX provided additional comments in a second submission which raised the following points:
  - The statement in the October 2002 Meeting Record of the Reasons "No further evidence was provided to support the assertions made that aflatoxins or other contamination and not neem itself caused the reported acute effects" was not valid. XXXXXXXXX claimed that data had already been provided to the TGA, demonstrating that cold pressed neem seed oil is not acutely toxic by the dermal and inhalation routes. On this basis, any neem oil showing significantly worse acute toxicity was most probably contaminated with some toxic foreign material and in addition, the safety of cold pressed neem seed oil was supported by a long history of use in India (>4000 years).
  - The acute oral LD_{50} values determined for neem oil from the three studies provided previously to the TGA (CNPM Branch) are:

    > 5g/kg (rats) for cold-pressed neem oil;
    11.8g/kg (rats) traditional neem oil;
    20.2 g/kg (rabbits) traditional neem oil;
    1.57 g/kg for XXXXXXXXX, a neem seed polar solvent extract; and
    > 5 g/kg for XXXXXXXXX neem seed (methanolic) extract.

    On the basis of these toxicity values, as well as the evidence of traditional use, cold pressed neem oil should be included in Schedule 5, as well as neem seed extracts, extracted using water, methanol or ethanol.
  - XXXXXXXXX appreciated the reasons for the Committee's recommendations relating to preparations for dermal use, given the concerns on reproductive toxicity. However, the products for which the company is seeking TGA approval contain 2% cold-pressed neem oil in a head lice shampoo or head lice spray presentation. XXXXXXXXX argued that it was not feasible to put child-resistant closures on shampoo bottles or on trigger-pack spray containers and that the 2% level, although long established as efficacious for head lice, would

become Schedule 6 poisons. The cut-off level set at 2% cold-pressed neem oil rather than 1% still provided a 50-fold safety margin.

- XXXXXXXXX supported the proposed new Schedule 5 & 6 entries for *Azadirachta indica* extracts.
- XXXXXXXXX sought reconsideration of October 2002 decision based on the following grounds:
  - **Inconsistency of Scheduling Decision**. The separation of neem extracts and its derivatives into different categories, i.e. exempt from scheduling, Schedule 5 and 6, was inconsistent and arbitrary, and had no scientific basis. Whilst XXXXXXXXX did not agree with the decision to schedule neem derivatives for agricultural use, it recommended that all neem derivatives should be subject to a consistent scheduling decision and that all neem derivatives for agricultural use be either exempt from scheduling or included in Schedule 5.

    XXXXXXXXX agreed with CMEC that cold pressed neem seed oil should not be scheduled. If the cold pressed neem seed derivative was considered 'safe' for human dermal application, where it was applied in concentrated form, then there was no scientific basis for this very same substance to become 'toxic' when used in a very diluted form (0.5%) for agricultural purposes.

  - **Unbalanced Approach To Evidence**: The NDPSC's October 2002 Meeting *Record of the Reasons* gave undue weighting to unsubstantiated claims as to the putative toxicity of neem derivatives, which relied on two discredited case studies. In XXXXXXXXX submission to the NDPSC, it provided argument to suggest that the alleged 'acute oral toxicity' of neem derivatives was not supported by scientific evidence. The Committee appeared to have disregarded these arguments and failed to provide any valid scientific evidence supporting the case for the scheduling of neem derivatives for agricultural purposes.
  - XXXXXXXXX urged the NDPSC to reconsider its decision and exempt neem derivatives for use in agriculture, which would be consistent with the broader scientific, epidemiological and public health data. With the exception of neem used in internal human applications, there were insufficient grounds to support the scheduling of neem derivatives as either Schedule 5 or 6 substances.

- XXXXXXXXX first submission stated that there was no historical basis for the acute toxicity effects associated with neem or its extracts in humans or mammals nor was there any evidence of reproductive impairment.
- XXXXXXXXX and XXXXXXXXX raised the following points in a second submission:
  - The Committee did not attempt to clarify why a similar exemption had not been extended to 1% neem oil for agricultural use.

- Quality standards had not been established to ensure purity of neem seed oil imports, which should include a requirement for Aflatoxin-Free Assurance Certificate.

- XXXXXXXXX opposed the proposed scheduling of neem as a toxic or poisonous substance when it was beneficial to humanity when used sensibly and responsibly. The submission claimed that neem derivatives could be used in every state of the USA for crop protection and the FDA regarded neem as a 'safe' substance while the Committee regarded it as a poison.
- In a second submission, XXXXXXXXX stated that whilst they were opposed to the October 2002 decisions on neem, it also recognised that the NDPSC would draw its own conclusions and XXXXXXXXX would abide by those decisions. However, to facilitate compliance, XXXXXXXXX sought an extension of the implementation date from 1 May 2003 to 1 September 2003, to allow sufficient time for the industry to manage the necessary changes.
- XXXXXXXXX agreed that the registration of all extracts for agricultural and veterinary use should be dealt with through the NRA, given that such products contained high percentages of azadirachtins and other limonoids. XXXXXXXXX was opposed to the scheduling of neem for human use, on the grounds that Ayurvedic medicine continued to use the bitters of the neem seed as well as the neem leaves in combating infection, internal and external.
- XXXXXXXXX supported the decision and considered the Committee objective in its findings.

The Committee also noted the following additional comments received:

- XXXXXXXXX sought a six-month extension of the implementation date to sell his remaining stocks.
- XXXXXXXXX supported and welcomed the Committee's decision to exempt from scheduling cold pressed neem seed oil at 1 % for human dermal use but requested that this exemption be extended to include preparations for agricultural use diluted to contain 1 % cold pressed neem seed oil.
- XXXXXXXXX welcomed the Committee's decision to exempt from scheduling cold pressed neem seed oil at 1% for human dermal use but also proposed to exempt cold pressed neem seed oil for agricultural use, to be diluted on a farm at a ratio of 1:200 (0.5%).

Other issues raised in post-meeting submissions included:

- Cold pressed neem seed oil is an efficacious pesticide for agricultural use and a better product compared to aqueous or methanolic extracts from neem.
- Economic considerations.

- Lack of expertise in the area of agricultural science within the NDPSC to make sound scheduling decisions on neem.
- Claims that the Committee did not consider all public submissions provided at October 2002 meeting.
- The scheduling of neem in Australia was contrary to the global attitude where the use of natural products in lieu of synthetic chemicals was being actively encouraged.
- The NDPSC did not provide sufficient evidence to the public to support its scheduling decision.

Members noted that whilst the majority of the post-meeting comments received disagreed with the scheduling of neem, no new data or information were provided to address the grounds underpinning the October 2002 decisions on *Azadirachta indica* stated in the Record of the Reasons. The Committee noted that a substantial amount of information including the expert evaluations prepared for the NDPSC and CMEC, and their supporting bibliographies, was made available to the public via the NDPSC website to assist stakeholders in addressing the toxicity issues raised. However, members stated that the concerns in relation to reproductive and antiandrogenic effects and foetotoxicity, and the potential for acute toxicity in children remained unresolved. Furthermore, the Committee pointed out that scheduling decisions were based on public health and safety matters set out in s.52E of the *Therapeutic Goods Act 1989* (the Act) and not on economic grounds.

Members noted that the significant potential for adverse reproductive and fertility effects associated with neem exposure were not considered a serious public health concern by some post-meeting respondents, based on the claim that these were reversible effects therefore, not a permanent impairment. The Committee highlighted that neem products currently available on the market were required to be registered to ensure appropriate controls to minimise the risks to public health. The Committee again expressed its concern in regard to the general perception that products derived from 'natural' sources should not attract any restrictions similar to those imposed by scheduling, on the belief that they were inherently 'safe'.

The proposal by XXXXXXXXX to extend the cut-off to 2% for dermal preparations was not supported. The existing 1% cut-off was based on a minimum 100-fold safety factor from the neat cold pressed neem seed oil, which was already considered to be an extrapolation to the limits of the available meagre information. Therefore, the Committee was not prepared to reduce this safety margin until such time that neem and its extracts were fully characterised and the toxicology fully understood, and data became available to demonstrate safety at the proposed 2% level.

The proposal that products containing 0.5-1% cold pressed neem seed oil for use in agriculture be exempt from scheduling was also not supported. The Committee found no compelling argument to amend the recommended scheduling of neem to allow the exemption of such products as there was no impact on existing registered products for agricultural use. The Committee clarified for the benefit of many respondents that the

scheduling of a substance and cut-offs for exemption specified in the Schedule entries of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) applied to products packaged for sale in the domestic market, not to dilute preparations derived from such products for on-farm use.

The Committee noted that no grounds other than economic hardship were provided to warrant a delay in the implementation date of the October 2002 decision on neem. In the absence of any argument fulfilling the criteria set out in s.52 of the Act, the Committee considered the seven-month interval between making the decision (October 2002) and the date of effect, i.e.1 May 2003, was sufficient to allow the necessary labelling changes to take place.

Members noted that the neem scheduling proposal contained no requirement for Schedule 5 and 6 neem products to be fitted with a Child-Resistant Closure (CRC) specified in Part 2 of the SUSDP. It was agreed that this was inconsistent with the intent of the Committee and that the inclusion of a requirement for CRC on containers for Schedule 6 neem products in liquid form should be formally considered at the June 2003 meeting. The Committee did not support the proposal to require CRC on Schedule 5 products, on the grounds that agricultural products included in Schedule 5 were unlikely to be used in the home setting and unlikely to be available in small volumes typical of products for domestic use.

OUTCOME

The Committee agreed to foreshadow, for consideration at the June 2003 meeting, the inclusion of a requirement for CRC in Part 2 of the SUSDP for *Azadirachta indica* (neem) including its extracts or its derivatives in liquid form when included in Schedule 6 of the SUSDP to allow adequate time for public consultation.

FORESHADOW

Part 2, Section 25(1) of the SUSDP – New entry

Azadirachta indica (neem) including its extracts or its derivatives in liquid form when included in Schedule 6.	2 litres or less

DECISION 2003/37 - 21 , Confirmation of DECISION 2002/36 – 15.

The Committee confirmed its October 2002 decision that *Azadirachta indica* (neem) or its extracts or its derivatives:

(i) in preparations for human internal use except 'debitterised neem seed oil' be included in Appendix C of the SUSDP;
(ii) be included in Schedule 6 (base Schedule);
(iii) when 'debitterised' be exempt from scheduling;

(iv) in preparations containing cold pressed neem seed oil for human dermal use, labelled with the recommended warning statements and fitted with a child resistant closure be exempt from scheduling;
(v) in preparations for human dermal use containing 1% or less of cold pressed neem seed oil be exempt from scheduling;
(vi) preparations when included in Schedule 6 should be labelled with Appendix F Warning Statement 67 (Do not use if pregnant or likely to become pregnant); and
(vii) extracted from seed kernels using water, methanol or ethanol contained in preparations for agricultural use containing 5 per cent or less of total limonoids be included in Schedule 5.

The Committee confirmed that the decision was based on the following rationale:

(i) There was clear evidence of reproductive toxicity and antiandrogenic effects in experimental animals, and acute toxicity in humans to warrant prohibition of all human internal use of neem products until sufficient evidence is available to characterise the substance(s) responsible for the toxicity.

(ii) The toxicity profile including acute, reproductive and foetal toxicity which was seen generally over a range of preparations and extracts based on the neem tree, was appropriate for inclusion in Schedule 6 of the SUSDP for all other uses.

(iii) The Committee agreed to exempt 'debitterised' neem seed oil from scheduling on the basis that highly purified neem oil containing only fatty acids and glycerides of fatty acids is unlikely to cause toxicity. This conclusion was supported in part by toxicity data relating to highly purified neem seed oil which showed no adverse effects.

(iv) The Committee accepted CMEC's recommendation relating to products containing cold pressed neem seed oil for topical use on the skin, and was of the view that there was scope for exempting such products. However, the Committee has remained sufficiently concerned over the potential for dermal absorption and the possible reproductive and foetotoxic effects from dermal exposure, that it has agreed to exempt such products only when labelled with "Do not use if pregnant or likely to become pregnant". This label would be in addition to CMEC's recommended label warnings and requirement for CRC on products.

(v) The reproductive toxicity of concern to the Committee was associated with the 4-5% non-lipid fraction of the cold pressed neem seed oil. The Committee is confident that allowing an exemption for dermal products containing 1% or less of the cold pressed neem seed oil should provide an adequate safety margin against reproductive toxicity, based on the further 1:100 or greater dilution of the neat cold pressed neem seed oil in such products. Other extracts from the neem seed or other parts of the neem tree were not given a similar exemption to the cold pressed neem seed oil, due to concerns that the uncharacterised reproductive toxicants may be

inadvertently concentrated during processing of such extracts. No adequate compositional and toxicological data on extracts and preparations other than cold pressed neem seed oil were available to the Committee to allow further consideration of the other extracts or other parts of the neem tree.

(vi) The Committee has agreed that *Azadirachta indica* (neem) or its extracts or its derivatives in Schedule 6 should be labelled with Appendix F Warning Statement 67, based on neem's reproductive, antifertility and foetotoxic effects in experimental animals and humans.

(vii) Based on the available acute toxicological data and in-furrow use which minimised operator exposure, the Committee confirmed inclusion in Schedule 5 of *Azadirachta indica* extracts, extracted from neem seed kernels using water, methanol or ethanol, in preparations containing 5 per cent or less of total limonoids, for agricultural use.

Appendix C – New entry

AZADIRACHTA INDICA (neem) including its extracts or its derivatives, in preparations for human internal use **except** debitterised neem seed oil.

Schedule 6 - New entry

AZADIRACHTA INDICA (neem) including its extracts or its derivatives **except**:

(a) in preparations for human internal use;

(b) when included in Schedule 5;

(c) 'debitterised neem seed oil';

(d) in preparations for human dermal therapeutic use containing cold pressed neem seed oil, when in a container fitted with a child resistant closure and labelled with the statements:

" Not to be taken"

"Keep out of the reach of children"

"Do not use if pregnant or likely to become pregnant"; or

(e) in other preparations for dermal use containing 1 per cent or less of cold pressed neem seed oil.

Schedule 5 - New entry

AZADIRACHTA INDICA EXTRACTS (neem extracts), extracted from neem seed kernels using water, methanol or ethanol, in preparations containing 5 per cent or less of total limonoids, for agricultural use.

Appendix E, Part 2 – New entry

AZADIRACHTA INDICA (neem) including its extracts or its derivatives when included in Schedule 6.

Standard Statement …….A, E1

Appendix F, Part 3 – New entry

AZADIRACHTA INDICA (neem) including its extracts or its derivatives when included in Schedule 6.

Warning Statement …….67

Part 1, Interpretation – New entry

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

12.2 POLYACRYLAMIDE

PURPOSE

The Committee considered post-meeting comment concerning the decision made at the October 2002 meeting to include polyacrylamide in Schedule 4 (S4) of the SUSDP.

BACKGROUND

The October 2002 NDPSC Meeting agreed to include polyacrylamide in preparations for injection or implantation for tissue augmentation or cosmetic use in S4. This decision was made in order to minimise the potential public health hazard arising from use of such products, by requiring:

- professional examination and counselling prior to use;
- medical supervision of technique, procedures and siting during use; and
- medical monitoring of post-procedural outcomes, adverse effects and long term sequelae.

DISCUSSION

The Committee noted the post-October 2002 meeting comments from XXXXXXXXX which claimed its submission was not fully and reasonably considered by the NDPSC at the October 2002 meeting and raised the following points in support of reconsideration:

- Polyacrylamide is not a drug nor a poison and no adverse effects have been reported for its subcutaneous implantation in accordance with the instructions for use.
- Such medical devices have been approved for entry to the ARTG and therefore, the Secretary is satisfied that they are safe for their intended purpose.
- If the NDPSC has evidence of harm caused by polyacrylamide or any other product used for tissue augmentation in accordance with the manufacturer's instructions, the appropriate course of action would be for this to be drawn to the attention of those responsible for medical device regulation in the TGA.
- If deemed appropriate, conditions could be applied to products for injection or implantation for tissue augmentation or for cosmetic use on the ARTG which limit their sale and use to medical practitioners.
- The ramifications of the scheduling of polyacrylamide for a medical device supplier are major and unreasonable. For example, the need to obtain a NSW poisons license and the establishment of secure storage and distribution for a product that is neither harmful, poisonous nor dangerous.
- Many products are sold which claim to, or do, penetrate the skin for the same indications as the products for which the NDPSC is pursuing scheduling.
- Subcutaneous injection does not necessarily make a substance more hazardous than those that permeate through the skin.
- The NDPSC is requested to provide the evidence to support the basis for scheduling, i.e. that polyacrylamide represents a hazard.

The Committee noted that polyacrylamide is a listable excipient in sunscreen preparations and is also included in devices in the Australian Register of Therapeutic Goods (ARTG).

The Committee accepted that the toxicological profile might be appropriate for an unscheduled product. However the Committee emphasised that much more than the toxicological profile was considered in scheduling a substance, including its proposed use, the way it is used, and the potential for adverse effects.

The Committee was advised that the regulatory options under the registration scheme to restrict the availability and advertising of injectable dermal fillers were limited where the product is unscheduled. However, appropriate controls were available once a product was scheduled.

The Committee was aware that polyacrylamide in preparations for injection or implantation for tissue augmentation or cosmetic use was administered using a physically invasive technique and had concerns with the level of knowledge and training with respect to injection/implantation techniques, the appropriate use of infection control

procedures, the degree of patient follow-up undertaken, and the monitoring and treatment of any adverse effects. The members noted that at present, medically unqualified persons were able to supply and administer these products to the consumers. The risk of uncontrolled administration via invasive procedures was judged by the Committee to be a serious potential public health hazard and the Committee considered it appropriate to limit the procedure to medical professionals. Members also noted the "Instructions for Use" found on the XXXXXXXXX Internet site stated that a local anaesthetic might be required before the introduction of the product supporting the view that safe use requires use by medical professionals.

The Committee reaffirmed its view that professional examination and counselling were essential prior to use. Further, patients were unlikely to be able to objectively balance the advantages against any risks for this particular treatment. The Committee agreed that this rendered direct-to-consumer advertising highly undesirable.

The Committee noted that the Internet information on the product XXXXXXXXX stated there were no serious adverse events arising from an interim clinical trial report in Europe. However the Committee observed that adequate avenues for reporting toxicity might not be available for an unscheduled product. Again the Committee reiterated that it was not the inherent toxicity of the substance that was at issue but the way it was being used and the potential for adverse reactions that were the major concerns. The Committee agreed that the use by medically unqualified persons would likely result in an under-reporting of any adverse events and therefore limit the ability of the manufacturer and regulatory bodies to become aware of adverse events associated with the use of product. These concerns were supported by the information contained in the "Consent Form" and "Instructions for Use" on the XXXXXXXXX Internet site.

Overall the Committee reiterated that polyacrylamide in preparations for injection or implantation for tissue augmentation or cosmetic use clearly met the classification criteria for inclusion in Schedule 4. While the Committee was aware of XXXXXXXXX argument in relation to the economic restraints that inclusion in S4 may incur, members noted this was not a matter required to be taken into account in the scheduling of a substance.

DECISION 2003/37 - 22

The Committee confirmed the Decision 2002/36-16 from the October 2002 meeting to include in Schedule 4 polyacrylamide in preparations for injection or implantation for tissue augmentation or cosmetic in order to protect public health by taking into account:

- the potential hazards associated with the use of this substance;
- the extent and patterns of use of a substance; and
- the risks of injury or illness resulting from its use.

The Committee agreed the product:

- requires professional examination and counselling prior to use;
- requires medical supervision of technique, procedures and siting during use;
- requires medical monitoring of post procedural outcomes, adverse effects and long term sequelae; and
- should not be advertised direct-to-consumer.

The Committee confirmed the overall classification profile was appropriate for inclusion in Schedule 4.

Schedule 4 - New entry

POLYACRYLAMIDE in preparations for injection or implantation:

(a) for tissue augmentation; or

(b) for cosmetic use.

13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

13.1 CLOBETASONE, ALCLOMETASONE AND HYDROCORTISONE

PURPOSE

The Committee reviewed the Schedule 3 (S3) entries for clobetasone and alclometasone in relation to whether these entries should be limited to single active ingredients only.

BACKGROUND

Hydrocortisone and hydrocortisone acetate was first included in S3 at a concentration of 0.5% or less when present as the only therapeutically active substance at the August 1985 meeting. The February 1999 meeting amended the S3 entry to include preparations containing 1% or less of hydrocortisone either alone, or in combination with an antifungal. The Committee did not support the proposal to allow all combination products containing hydrocortisone as hydrocortisone can increase the dermal absorption of other therapeutic agents.

The March 1980 meeting first included clobetasone in S4. The February 2002 meeting agreed to include clobetasone when in preparations for dermal use containing 0.05% or less of clobetasone in packs containing 30 g or less in Schedule 3 on the basis of its safety profile.

The May 1988 meeting first included alclometasone in S4. The February 2000 meeting agreed to reschedule alclometasone in preparations for dermal use containing 0.05 per

cent or less of alclometasone in packs containing 30 g or less of such preparations to S3 on the basis of its safety profile.

The relative potencies of clobetasone and alclometasone are comparable and the safety profile and efficacy of 0.05 per cent alclometasone is similar to 1 per cent hydrocortisone. Following the October 2002 meeting the Secretariat noted a discrepancy in regard to limitations placed on S3 combination products for hydrocortisone, clobetasone and alclometasone.

DISCUSSION

A member recalled that safety data for combination products was not considered in the scheduling of clobetasone and alclometasone at recent meetings. The member preferred to discourage combination products as antibacterial /steroid use is recommended only when necessary and not on a regular basis. The member also considered it appropriate to limit the entries to single-active formulations only and suggested that if other ingredients are to be included, a sponsor should justify the safety of these combinations and interested parties could be given the opportunity to comment. Members expressed concern over some of the potential combinations.

The Committee noted there were two registered products containing alclometasone as a single active ingredient and no registered products containing clobetasone on the ARTG. The Committee expected no adverse commercial impact or regulatory impact if the clobetasone and alclometasone S3 entries were limited to single active ingredients.

The NZ member outlined NZ's position to classify combination products based on the highest scheduled ingredient, unless there was evidence that the combination of ingredients increased toxicity or interaction, or increased absorption or changed the safety profile or may lead to inappropriate use. Members noted there was not a high degree of accuracy in the diagnosis of fungal infections either by medical practitioners or pharmacists, and often the combination preparation was selected as being the most appropriate. The Committee noted the Industry representative supported the NZ approach. The NZ member regarded safety and efficacy as a registration issue rather than a scheduling matter.

Members were concerned that combination products could effect the safety profile given the modifying effect of corticosteroid on other preparations and their potential for inappropriate use.

DECISION 2003/37 - 23

The Committee agreed to amend the Schedule 3 entries for clobetasone and alclometasone to limit them to single active ingredient formulations only, taking into account their existing safety profile. The Committee expressed a concern over the absence of safety data of combination products and considered it appropriate for future

applicants to provide adequate evidence of safety and efficacy to allow such combination products to be considered for inclusion in Schedule 3.

Schedule 3 – Amendments

CLOBETASONE – amend entry to read:

CLOBETASONE (clobetasone-17-butyrate) as the only therapeutically active substance in preparations for dermal use containing 0.05 per cent or less of clobetasone in packs containing 30 g or less of the preparation.

ALCLOMETASONE – amend entry to read:

ACLOMETASONE as the only therapeutically active substance in preparations for dermal use containing 0.05 per cent or less of alclometasone in packs containing 30 g or less of the preparation.

13.2 PSEUDOEPHEDRINE

PURPOSE

The Committee continued its consideration of the scheduling of pseudoephedrine in undivided, combination and slow release preparations in Schedule 2 (S2) of the SUSDP.

BACKGROUND

The June 2002 Meeting agreed to reschedule all OTC single-active immediate release preparations from S2 to S3, to help address the on-going problem of diversion of these products to the illicit drug trade, and foreshadowed consideration of the scheduling of remaining S2 formulations at the October 2002 Meeting. However, the information available at the October meeting was considered inadequate to support scheduling action and members agreed to defer further consideration to the February 2003 meeting, and await the outcome of investigations on the extractability of all OTC pseudoephedrine products being coordinated by XXXXXXXXX. It was recognised that the data from these investigations would be critical in developing a better understanding of the extractability of pseudoephedrine from undivided, combination and slow release preparations in S2. In addition, the October 2002 Meeting also agreed that sponsors be asked to advise of their plans for existing and future product lines, particularly in relation to 'bilayer' formulations, due to concerns that the product presentation could make them attractive for diversion.

DISCUSSION

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

- XXXXXXXXX advised that a National Working Group on Diversion of Chemical Precursors (NWG) convened in November 2002, had identified two areas which were considered crucial in addressing illicit purchase activity, i.e. consistency of best practice across all pharmacies in Australia and research into the ease of pseudoephedrine extraction/conversion. It was indicated that a research plan to determine the differences in the extractability of pseudoephedrine from various presentations had been developed and the investigation was anticipated to be completed by mid-2003. XXXXXXXXX stated that any change in scheduling at this time would be premature and that sufficient time should be given to allow changes in pharmacy behaviour to occur.

In response to the NDPSC's concerns on bi-layer preparations, XXXXXXXXX requested that no scheduling action be taken on this formulation at this time given the lack of robust evidence of specific risk represented by XXXXXXXXX. XXXXXXXXX also argued that the bilayer nature of the product was not communicated in any promotional material, and unlike some similar products, the two layers were not visually discernible.

- XXXXXXXXX opposed any changes to the current scheduling of pseudoephedrine on the grounds that scheduling was not the appropriate mechanism for solving the diversion problem and that access to pseudoephedrine products must be maintained for legitimate users. XXXXXXXXX also stated that there was no evidence identifying the pharmacy as the point of diversion to support any changes to the scheduling of pseudoephedrine.

XXXXXXXXX also stated that it was not aware of any data to support the contention that 'bilayer' preparations were being targeted for diversion, due to the ease by which pseudoephedrine could be extracted, and it would be premature to make any rescheduling decisions based solely on preliminary data.

- XXXXXXXXX opposed any further restrictions on pseudoephedrine-containing products and considered the June 2002 meeting decision to restrict access to single-active ingredient products flawed. XXXXXXXXX stated that it had no plans of modifying XXXXXXXXX formulation based on economic grounds, and advised that the product was not considered a 'bilayer' preparation. In addition, it was indicated that the sales data for XXXXXXXXX did not suggest that it was being targeted for diversion.
- XXXXXXXXX reaffirmed its earlier statement that further scheduling of pseudoephedrine was inappropriate at this time, and stated that the national strategies and initiatives currently being undertaken should be given an opportunity to take effect.
- XXXXXXXXX supported rescheduling of all remaining pseudoephedrine containing products in S2 to S3, to ensure such products were stored out of the reach of the public. In addition, XXXXXXXXX stated that this approach would provide an opportunity for consumers to be guided by the pharmacist in selecting the appropriate pseudoephedrine product.

- XXXXXXXXX stated that the S2 availability of pseudoephedrine combination products to the legitimate consumer should be maintained on the interim however, additional controls should also be adopted. XXXXXXXXX recommended that pseudoephedrine combination products should be stored behind the counter and dispensed under pharmacist supervision at all times, and photo-identification be asked from consumers wishing to purchase such products. In addition, XXXXXXXXX also recommended that the Victorian approach relating to sale of pseudoephedrine products be adopted nationally.
- XXXXXXXXX reiterated its view that rescheduling of single-active pseudoephedrine preparations to S3 should be applied to all remaining products in S2, including all modified release and combination products, and that any scheduling decisions should be evidence based. XXXXXXXXX stated that restricted access was being arbitrarily imposed on some combination products whilst similar products remained unrestricted due to confusion within community pharmacies. It was indicated that these arrangements lead to commercial inequity due to differential restrictions being imposed on combination products, which could only be compounded by the separation of pseudoephedrine-containing products into different Schedules. XXXXXXXXX argued that unless direct evidence was available to show that a specific combination with other active ingredients directly inhibited the extraction of pseudoephedrine, combination products should be treated similarly to single-ingredient products.

XXXXXXXXX also advised that they had no plans to reformulate XXXXXXXXX, given that there was no evidence to suggest this formulation was being targeted for diversion.

The Committee noted that the XXXXXXXXX had recently endorsed a Code of Practice, which applied to the handling of all products containing pseudoephedrine. It was stated that the Code was designed to ensure that pharmacists continued to provide the most appropriate medicines and therapeutic advice to patients, without inadvertently contributing to the continuing problem of diversion of pseudoephedrine-containing products.

The Committee was advised that the XXXXXXXXX supported the view that the NDPSC should provide sufficient opportunity for national initiatives to take effect before taking further scheduling action.

The XXXXXXXXX advised that interim authorisation for the implementation of the ASMI Code of Conduct was granted by the ACCC on 13 February 2003. The member also stated that XXXXXXXXX would be providing regular updates to the Committee regarding the implementation of the Code of Conduct and its impact on the problem of diversion of pseudoephedrine-containing products.

Members informed the Committee that purchases of pseudoephedrine products by pharmacies and bulk sales made by pharmacists were being monitored in the jurisdictions, as part of on-going initiatives to help identify the point of diversion.

However, members felt that the data available at the time was insufficient from which to draw unequivocal conclusions.

Several jurisdictions again reported that combination products continued to be found in clandestine laboratories although it could not be established whether pseudoephedrine was extracted successfully from such products.

A member raised the issue of whether the current dose levels of pseudoephedrine for OTC indications were necessary to achieve therapeutic efficacy. It was argued that if it was established that lower dose levels were efficacious in OTC indications, then there may be grounds for requiring OTC products to be reformulated to contain lower amounts of pseudoephedrine, thus making them less attractive for diversion.

OUTCOME

The Committee agreed to defer further consideration of the scheduling of remaining pseudoephedrine-containing preparations in Schedule 2 to the June 2003 meeting. The Committee considered that more time was required to allow for the findings of the investigations currently being undertaken to determine the extractability of pseudoephedrine from various OTC formulations to become available.

The Committee agreed that previous submissions relating to this matter will be carried forward to the June 2003 meeting and the persons who made the submissions will be eligible to comment on any decisions made at the June 2003 meeting.

The Committee also agreed to seek advice from MEC on the effectiveness of the current dose levels of pseudoephedrine in OTC indications and whether such doses could be reduced to achieve the same level of efficacy.

13.3 COLLAGEN, HYALURONIC ACID, POLYLACTIC ACID

PURPOSE

The Committee considered amending the Schedule 4 (S4) entries for collagen, hyaluronic acid and polylactic acid to include preparations for implantation.

BACKGROUND

The October 2002 meeting agreed to include polyacrylamide in preparations for injection for tissue augmentation or cosmetic use in S4 of the SUSDP. This was based on the view that minimisation of the potential public health hazard associated with use of the product requires:

- professional examination and counselling prior to use;
- medical supervision of technique, procedures and siting during use; and

- medical monitoring of post-procedural outcomes, adverse effects and long term sequelae.

The Committee was also advised that similar substances for tissue augmentation and cosmetic use might be either injected or implanted. The Committee agreed to clarify the intent of S4 entries for substances used in tissue augmentation or cosmetic use, to encompass preparations for injection or implantation (collagen, hyaluronic acid and polylactic acid).

DISCUSSION

The Committee noted that a pre-meeting submission had been received from the XXXXXXXXX which reiterated its interest in ensuring that the scheduling of polylactic acid does not impact on existing topical and cosmetic products.

The Committee also noted the current products included in the ARTG for use in tissue augmentation were S4 products and that the proposed amendments to include preparations for implantation would have no regulatory impact.

DECISION 2003/37 - 24

The Committee agreed to amend the entries for collagen, hyaluronic acid and polylactic acid in Schedule 4 to clarify the intent that preparations for injection or implantation for tissue augmentation or cosmetic use are included in Schedule 4.

Schedule 4 – Amendments

COLLAGEN – amend entry to read:

COLLAGEN in preparations for injection or implantation:

(a) for tissue augmentation; or

(b) for cosmetic use

HYALURONIC ACID – amend entry to read:

HYALURONIC ACID in preparations for injection or implantation:

(a) for tissue augmentation; or

(b) for cosmetic use

POLYLACTIC ACID – amend entry to read:

POLYLACTIC ACID in preparations for injection or implantation:

(a) for tissue augmentation; or

(b) for cosmetic use

13.4 IRON COMPOUNDS

PURPOSE
The Committee considered amending the Schedule 2 (S2) entry for iron compounds to clarify the cut-off for exemption for iron oxides when present as an excipient.

BACKGROUND

The October 2002 NDPSC Meeting considered a request for clarification relating to the S2 entry for iron compounds, specifically in relation to iron oxides when present as an excipient. The Committee noted that the existing S2 cut-off for exemption for iron oxides only applied to preparations containing **less** than 10mg of total iron oxides in divided preparations, or **less** than 1% of total iron oxides in undivided preparations. Members agreed that the existing wording did not reflect the intent of the Committee to apply the cut-off for exemption for iron oxides to preparations containing exactly 10 mg of iron oxides (divided preparations) and 1% of iron oxides (undivided preparations). The Committee agreed to gazette the proposal to amend the S2 entry for iron compounds to address this inconsistency for consideration at the February 2003 meeting.

DISCUSSION

The Committee noted the pre-meeting submission XXXXXXXXX stating that they did not object the proposed amendment to the S2 entry for iron compounds to clarify the cut-off for iron oxides when present as an excipient.

DECISION 2003/37 – 25

The Committee agreed to amend the Schedule 2 entry for iron compounds to clarify the Committee's intent to apply the exemption for iron oxides when present as an excipient in divided preparations containing 10mg or less of total iron oxides per dosage unit and undivided preparations containing 1 per cent or less of total iron oxides.

Schedule 2 – Amendment

IRON COMPOUNDS – amend entry to read:

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

(a) when included in Schedule 4; or

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

(i) in undivided preparations supplied in packs each containing 600mg or less of iron; or

(ii) in divided preparations:

(A) containing more than 5mg of iron per dosage unit in packs each containing 600mg or less of iron; or

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

13.5 (DELETED)

13.6 OXEDRINE

PURPOSE

The Committee finalised its consideration of the scheduling of oxedrine. (synephrine).

BACKGROUND

Oxedrine (syn. synephrine) is a sympathomimetic amine occurring naturally in some Citrus species including *Citrus aurantium, Citrus sinensis* and *Citrus limon*, and in some cacti, e.g. *Coryphantha macromeris* and *Dolichotele* spp. Oxedrine has a similar pharmacology to ephedrine but is devoid of central nervous system (CNS) effects. The vasoconstrictor effect of synephrine is known to be due to activation of α-adrenoceptors.

The February 2002 NDPSC Meeting was requested to consider the scheduling of oxedrine and was advised that products containing significant amounts of oxedrine from *Citrus aurantium* and its extracts were being advertised on the Internet making therapeutic claims. These products were being marketed as diet supplements claimed to support metabolism, burn body fat and for weight loss. The NDPSC subsequently referred the matter back to the Office of Complementary Medicines (OCM) for further investigation and advice.

The October 2002 NDPSC Meeting considered the scheduling of oxedrine following receipt of advice from OCM stating that there were approximately 1000 complementary products listed on the Australian Register for Therapeutic Goods (ARTG) containing possible amounts of oxedrine in the recommended daily dose ranges of 2 µg to over 31 mg. At this meeting, the Committee expressed a concern with the risks associated with oxedrine as a sympathomimetic agent and its potential to cause cardiovascular toxicity.

However, the NDPSC deferred the scheduling of oxedrine to the February 2003 meeting to permit comment and provision of information on which a cut-off to exempt products could be based. Accordingly, the Committee agreed to seek the following information from stakeholders for consideration at the February 2003 meeting:

- the extent to which oxedrine is being used as an active ingredient;
- the purposes for which oxedrine is being used;
- the relationship of oxedrine dose with risk of toxicity including cardiovascular effects; and
- the overall pharmacology of oxedrine.

DISCUSSION

The Committee noted that XXXXXXXXX raised the following points in its pre-meeting comments:

- Oxedrine appeared in a large number of complementary medicine products for both internal and external use. There was no evidence to suggest that pure oxedrine was used in the manufacture of products but rather, extracts of *citrus aurantium* and other citrus species were being used. One raw material supplier in the United Sates was known to offer extracts containing oxedrine at 4%, 6%, 10%, 30% and more.
- The main use of oxedrine was in over the counter health supplements and weight loss products.
- With regard to dose vs. risk of toxicity, Martindale described the therapeutic dose in treatment of hypotensive states as "about 100 mg three times daily". There was little evidence of harmful effects at the dosage levels achieved in products of 30 mg in divided dose daily or below. The XXXXXXXXX once listed oxedrine as a substance banned for use in sport, however XXXXXXXXX understood that oxedrine was recently removed from the XXXXXXXXX prohibited list.
- Any sympathomimetic agent (even caffeine) had the potential to cause adverse effects on certain individuals. People with severe hypertension, cardiac disorders, glaucomas, and those taking some medications (e.g. MAO inhibitors and pseudoephedrine cough and cold preparations) should avoid consumption of oxedrine. These concerns could be addressed by including warning statements on labels, and the CMEC was the appropriate body to consider such statements including the pharmacology of herbal sources of oxedrine.
- XXXXXXXXX recommended that oxedrine in products for internal use be exempted from poisons scheduling when present in raw herbs and herbal extracts used in the manufacture of therapeutic goods up to a concentration of 10%, where the maximum permitted total daily dose was 30 mg or less. In addition, oxedrine in products for external use be exempted completely (it was present in essential oils of citrus which

were used in aromatherapy, cosmetics and toiletry preparations and other topical products).

The OCM advised the Committee in its pre-meeting comment that:

- OCM was aware of only four herbal species currently included in the ARTG as listed medicines where there was more definitive evidence that one or more parts of the plant may contain oxedrine (synephrine). These species were *Citrus aurantium* (bitter orange or seville orange), *Citrus sinensis* (orange), *Citrus limon* (lemon) and *Citrus unshiu* (chinpi). OCM also advised that there were reports of some psychoactive cacti, *Coryphantha macromeris*, and several species of *Dolichothele* which may also contain synephrine and/or alkaloids of synephrine however, none of these species were contained in existing products listed on the ARTG.
- Most of the herbs/plants listed had a long history of safe use however, it was apparent that newer and more novel preparations of these plants were becoming more popular, particularly those preparations which had the potential to concentrate certain components of the plant.
- Any scheduling of oxedrine in products for therapeutic use, including topical and oral administration, without limit on concentration had implications for over 1000 products currently listed on the ARTG. Whilst it may be appropriate to schedule oxedrine for therapeutic use, there was a need for consideration of an appropriate cut-off, perhaps combined with identification of, or exemption of, particular species or plant parts where synephrine was not known to be present.

The Committee noted that there was inadequate data available at the meeting to fully understand the pharmacological profile of oxedrine. Members also noted the data from an Italian study [G. Calapai et al, Fitoterapia 70 (1999) 586-592] indicated that the lowest observable effect level (LOEL) for oxedrine at which mortality/cardiotoxicity were seen was 2.5 mg/kg/day p.o in the rat. The estimated exposure of humans to oxedrine as a flavouring agent in extemporaneously prepared mixtures based on monographs in the Australian Pharmaceutical Formulary (17th Edition) was calculated to be 0.16-1.6µg/kg/day oxedrine per day.

Members highlighted that although there was no direct data available at the meeting to correlate the approximate dose of oxedrine and the likely adverse effects in humans, there was sufficient evidence to suggest the significant potential for oxedrine to cause cardiotoxicity at low dose levels. Furthermore, the Committee also noted that a 28-year old Australian man suffered a large myocardial infarction while abusing oxedrine tablets, although no data on the dosage level was provided in the case report.

A member proposed that a cut-off of 30 mg of total daily dose of oxedrine be adopted based on the value suggested by XXXXXXXXX. The Committee noted that the therapeutic dose given in Martindale was approximately 300 mg per day of oxedrine and that a 30 mg cut-off would provide a ten-fold safety factor.

DECISION 2003/37 - 26

The Committee agreed to include oxedrine for internal human use in Schedule 4 of the SUSDP except when the total daily dose is 30 mg or less of oxedrine, based on the following public health and safety grounds:

- Well-documented sympathomimetic nature of oxedrine and evidence to suggest that there was a significant potential for oxedrine to cause cardiotoxicity at low dose levels.
- There was inadequate data available at the meeting to demonstrate oxedrine's long term safety, given the potential for the substance to be taken for extended periods of time by consumers, e.g. herbal weight control preparations.
- The Committee was concerned with the potential public health risks associated with the uncontrolled availability of products containing increasing amounts of oxedrine.
- The cut-off to exempt products at 30 mg total daily dose of oxedrine should provide an adequate safety margin based on human clinical data.

Schedule 4 - New entry

OXEDRINE for human internal use **except** in preparations labelled with a recommended daily dose of 30 mg or less of oxedrine.

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

14.1 SUSDP, PART 4

14.1.1 LANSOPRAZOLE

PURPOSE

The Committee considered the scheduling of lansoprazole.

BACKGROUND

Lansoprazole is a proton pump inhibitor similar to omeprazole (S4) and pantoprazole (S4). It binds irreversibly to the proton pump on the mucosal membrane of the gastric parietal cells which inhibits gastric acid secretion, reduces the pH (acidity) of the gastric fluid reducing the pain associated with the reflux of gastric fluid into the lower oesophagus.

Lansoprazole was first considered for scheduling at the April 1994 meeting, when it was included in Schedule 4.

DISCUSSION

XXXXXXXXX submitted an application to reschedule lansoprazole oral dose forms containing not more than 30mg from S4 to S3 for the relief of symptoms of gastro-oesophageal reflux (heartburn) and acid-related dyspepsia (indigestion) in packs containing not more than 14 days supply from Schedule 4 to Schedule 3. In addition, inclusion in Appendix H of the SUSDP was sought.

The Committee noted the following points which the applicant highlighted in support of the proposal:

- Heartburn and indigestion are commonly experienced symptoms in the general population and can be easily recognised by sufferers. For many years, patients suffering heartburn and indigestion have self-medicated with OTC antacids and histamine-2 receptor antagonists (H_2RA). The safety and efficacy profile of lansoprazole represents a better choice compared to the other OTC treatment options

- Lansoprazole has no serious adverse events associated with its use based on large clinical trials and post-marketing data. The common adverse events such as headache, nausea and diarrhoea are self-limiting, easily managed and reversible. The absence of overdose reports in the literature and in post-marketing reports demonstrates lansoprazole's wide therapeutic window, therefore harmful effects from accidental or intentional overdose are unlikely. In addition, lansoprazole has a low drug-drug interaction risk.

- The risk of lansoprazole masking a serious disease is essentially no different to the risk associated with the OTC H_2RA products such as ranitidine and famotidine. By limiting the OTC pack size to no greater than 14 doses, serious conditions are unlikely to be masked, and their recurring symptoms are likely to prompt the patient to consult a doctor.

- XXXXXXXXX suggested two warning statements on the OTC label of lansoprazole products, on the grounds that it is not recommended for use in children or in women who are pregnant and breastfeeding. The proposed warning statements are:

  Seek medical advice before taking this product if you have liver disease, are pregnant, breastfeeding a baby or are hypersensitive to any of the ingredients in Zoton..

  Caution: this product is for the relief of minor and temporary aliments, and should be used strictly as directed. If symptoms persist, consult your doctor or pharmacist.

- Inclusion in Appendix H would allow advertising of lansoprazole which would create an awareness of the availability of an effective and safer alternative to the current range of OTC therapies. In addition, the proposed indication complies with the Therapeutic Goods Advertising Code.

- Additionally, letters of endorsement from XXXXXXXXX, XXXXXXXXX and XXXXXXXXX were received.

The Committee noted the following points from the evaluation report:

- Proton pump inhibitors are the most effective and most efficacious drugs for the initial and maintenance therapy of individuals with gastro-oesophageal reflux disease (GORD). Patients with GORD generally require chronic maintenance therapy and on-going medical supervision. Intermittent symptoms of acid-related dyspepsia and gastro-oesophageal reflux is a common problem in the community, however these symptoms do not fulfil the definition of GORD.

- The data, review material, guidelines and opinion contained in the application focused on the issue of GORD, but included little data on the proposed indication (dyspepsia and heartburn). The evaluator was not convinced that there is a need for proton pump inhibitors to be available over the counter for short-term self-medication.

- Independent reviews (Cochrane, NICE) showed no evidence to support the statement that proton pump inhibitors have any advantage over H_2RA in the proposed indication.

- Guidelines from the XXXXXXXXX do not support the use of proton pump inhibitors in individuals whose symptoms are not severe enough to meet the definition of GORD. The evaluator suggests that if the NDPSC considers the approval of this application, that the NDPSC may wish to consult with the XXXXXXXXX in order to ascertain its opinion of the appropriateness of the rescheduling of proton pump inhibitors to allow OTC use.

- Given lansoprazole's efficiency in severe GORD, there may be a risk of masking significant disease requiring medical management than the alternative preparations available for dyspepsia. If approved, it is suggested that the CMI be amended to include "alarm symptoms" that carry a higher risk of upper GI malignancy to reduce this risk. There should also be an additional warning that if three consecutive daily doses fail to provide relief of upper GI symptoms, then medical advice should be sought.

- The presence of food was associated with a 50% reduction in peak serum levels, a delay of 3.7 hours in achieving peak concentration and a reduction 27% in the extent of absorption of lansoprazole. To achieve optimal efficacy, lansoprazole should be administered on an empty stomach. This information should be included on both the label and the CMI, however it was only included in the proposed CMI and the information provided was inadequate.

- The benefits claimed for lansoprazole over the currently available OTC preparations concerning the absence of interactions with other drugs or food were not supported by the evidence provided and the benefit of rapidity of onset was not demonstrated for

the proposed indication. The long duration of action was seen as inappropriate for a drug used for intermittent management of symptoms likely to last only a few hours.

- Lansoprazole has a favourable safety profile, is not subject to abuse and is unlikely to cause significant consequences if misused. There were no specific safety concerns related to the drug itself in regard to rescheduling.

- Little evidence was submitted to support the inclusion of lansoprazole in Appendix H of the SUSDP other than statements used to support the rescheduling such as the clinical superiority of lansoprazole over H_2RA, the benefits of early treatment to prevent progression of reflux disease to erosive oesophagitis and the low risk of masking significant disease. There was no specific information provided to support that there would be a benefit to consumers, or to public health as a whole, as a result of inclusion of lansoprazole in Appendix H of the SUSDP.

- The evaluator did not support the application for the rescheduling of lansoprazole from S4 to S3 and recommends that it be retained in S4 for all uses.

- However, if the Committee considers the approval of this application, that the Committee consider amending the proposed S3 entry to include the dose limit (30mg) and restrict the entry to divided oral dose forms only.

The Committee noted the following pre-meeting comments:

- XXXXXXXXX supported the inclusion of lansoprazole in Schedule 3 as GORD is a reasonably commonly encountered complaint in the community pharmacy setting and there are resources available to pharmacists about GORD and related conditions as well as on the use of proton pump inhibitors (PPI). XXXXXXXXX also highlighted that it is vital for the sponsor to assist in disseminating current evidence-based information to the pharmacy profession, particularly in relation to the use of lansoprazole, if given S3 status. XXXXXXXXX did not support an Appendix H entry as there is currently no data or information concerning OTC use of this class in Australia.

- XXXXXXXXX objected to the rescheduling of lansoprazole on the grounds that it may mask more serious disease and believed that to reschedule this substance would be premature at this time.

- XXXXXXXXX opposed the rescheduling of lansoprazole until a self-diagnosis study, a usage study, a multicultural study, a comprehensive label study and a pharmacy education program are completed. The company also stated that there should be at least one year of pharmacy-only experience before inclusion in Appendix H.

- XXXXXXXXX did not consider the indications for lansoprazole appropriate for any form of self-diagnosis and requires medical management. XXXXXXXXX considered

the rescheduling of lansoprazole premature until such time that both the indication for S3 listing and an appropriate complementary education strategy are defined and developed. Listing of lansoprazole in Appendix H was also not supported.

XXXXXXXXX was concerned that consumers may not receive adequate on-going medical supervision if the product was available as an S3 medicine. The Member also raised concerns that consumers may delay seeking medical advice if taking lansoprazole and that the inclusion of the alarm symptoms in the CMI would not be sufficient to counter this. Although it was agreed that the terms indigestion, heartburn and reflux disease were used interchangeably by consumers, there was no evidence to suggest that consumers can appropriately self-diagnose, with the assistance of a pharmacist, to determine that lansoprazole is the most appropriate treatment when compared with other available treatments. Both the rescheduling of lansoprazole to S3 and its inclusion in Appendix H were not supported by XXXXXXXXX.

The Committee noted that all proton pump inhibitors are currently included in Schedule 4 in the SUSDP, therefore the rescheduling of lansoprazole would be the first rescheduling of this class of compounds.

The S3 indication sought by XXXXXXXXX is similar to the indication for the H_2RA's (famotidine, nizatidine, ranitidine and cimetidine) ie for the relief of symptoms of gastro-oesophageal reflux in packs containing not more than 14 days supply.

The S2 and S3 entries for the H_2RA's all require the warning statements 35, 68, 69 and 70. The Committee considered these warning statements in relation to the proposed rescheduling of lansoprazole to S3 for the proposed indication. The warning statements are listed below:

35. 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 aliments and should be used strictly as directed. Prolonged or excessive use without medical supervision could be harmful.

68. If symptoms persist beyond 5 days consult a doctor.

69. If symptoms recur within two weeks of completing the course, consult a doctor.

70. Use only under medical supervision if you are taking other medicines.

The Members agreed that patients can not always accurately diagnose these types of symptoms. It was noted that when a lay person describes their symptoms and say it is

acid or dyspepsia or indigestion, the may actually be describing GORD. There is also a difference in the lay use of the language compared with the technical use of the language.

A Member observed that the Committee has previously allowed products into S3 that require a medical diagnosis, on the basis that they be made available through a pharmacist once medical diagnosis had been made and a treatment regime started eg antifungal vaginal preps, salbutamol metered dose aerosols.

The Committee agreed that the evidence submitted by the sponsor showed that lansoprazole is effective when used in patients with proven GORD under medical supervision. However, the sponsor had not provided any data to support the OTC use of lansoprazole in cases where GORD has not been medically diagnosed. This was in distinct contrast to the H_2RA's where trials had been provided demonstrating effectiveness under OTC use. A conflict was also noted between the proposed dosage directions in the CMI and the proposed usage. The proposal for rescheduling was for symptomatic relief, however the CMI instructs the patient to take the medication with breakfast, not when they are symptomatic. This would be appropriate to preventative rather than symptomatic treatment. Further, where the data has shown relief, onset of relief was not immediate and may take up to 4-5 days. The Committee agreed that this was not appropriate for a short-term, symptomatic relief indication.

The data were submitted by the sponsor was inadequate to demonstrate efficacy for symptomatic relief of indigestion or heartburn. Although evidence of efficacy is primarily a registration issue, the Committee must take into account the purpose for which the substance will be used when assessing if it will be appropriately used if rescheduled.

The Committee expressed concerns that appropriate alarm symptoms were not adequately outlined in the CMI which it considers a safety issue with regard to the OTC use of this product.

OUTCOME

The Committee agreed that inclusion of lansoprazole in Schedule 4 remained appropriate at this time as:

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

- The Committee was not provided with sufficient evidence of efficacy for use in treatment of the symptoms of heartburn and dyspepsia as opposed to the treatment of GORD.

- The proposed indications for use, onset and duration of action were more appropriate to the prevention of symptoms rather than intermittent treatment of, or relief from, symptoms.

- There was a need to address appropriate alarm symptoms requiring medical investigation rather than ongoing intermittent self-medication.

14.1.2 KETOPROFEN

PURPOSE

The Committee considered an application seeking to exempt ketoprofen in preparations for dermal use from scheduling requirements.

BACKGROUND

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) which has been marketed for the treatment of rheumatoid arthritis and osteoarthritis in various forms (standard release capsules, sustained release capsules, suppositories and topical gels) since 1981.

XXXXXXXXX markets XXXXXXXXX containing 2.5% 25mg/g ketoprofen for the short-term (up to 7 days) treatment of musculo-skeletal inflammation and injury, such as sports injuries, sprains, tendonitis, musculotendinous contusions, swelling and post-traumatic pain.

The August 1999 NDPSC meeting agreed to rescheduled ketoprofen in preparations for dermal use from Schedule 4 (S4) to Schedule 2 (S2) to harmonise with New Zealand. Similar NSAIDs in preparations for dermal use, diclofenac, piroxicam and ibuprofen, have been exempted from scheduling at the February 2000 meeting, May 2000 meeting and October 2002 meeting respectively.

DISCUSSION

The Committee noted the following arguments were raised by XXXXXXXXX application to exempt ketoprofen in preparations for dermal use from scheduling:

- XXXXXXXXX (ketoprofen) has been registered in Australia since 1994 providing a local experience with the use of the product of over 8 years, exhibiting an excellent safety profile for this product over this period.

- Both diclofenac and piroxicam were exempted from scheduling for dermal use based on their safety profile and indications. The safety profile of topical ketoprofen is equivalent to these substances and the use is the same as for diclofenac and piroxicam.

- The conditions included in the indications XXXXXXXXX are of a short term and self-limiting nature and are suitable for self-selection. They are easily identified by the consumer and may be successfully treated without the need for professional advice.

- The adverse events reported for XXXXXXXXX are predominantly non-serious local reactions of limited extent, in contrast to the adverse events for oral NSAID therapy.

- Accumulation of ketoprofen is not known to occur and systemic exposure when topically administered is around one hundred times lower than local exposure.

- The abuse potential is extremely low. Ketoprofen is not associated with any stimulating or euphoric effects and the entire contents of a tube are insufficient to cause a life-threatening adverse event.

The Committee noted from the evaluation report of the applicant's submission that:

- Ketoprofen, when administered topically, has a very low systemic bioavailability and causes very few adverse effects, which were also, the case for diclofenac and piroxicam. Ketoprofen has a very low to absent potential for abuse. Inappropriate topical use is extremely unlikely to result in any systemic adverse events.

- The indication for topical administration of ketoprofen is suitable for self-identification and treatment without professional advice.

- Topical piroxicam and diclofenac products have been exempt from scheduling for approximately 2 years with no significant safety issues arising over that time. It is unlikely that the exemption of ketoprofen for topical use would cause any additional clinical problems.

- There is considerable marketing experience with dermal ketoprofen within Australia and the spontaneous reporting of adverse events has been very low. Post-marketing surveillance suggests that the topical preparation is very safe in over the counter use.

- There may be a case for including warnings on the labelling concerning use by persons allergic to NSAID’s or at risk of NSAID-induced exacerbation of asthma, although these warning are included on the proposed CMI.

- There are no public health considerations in relation to the exemption of topical ketoprofen, given the current availability of topical NSAID’s with very similar characteristics in normal use.

- The evaluator recommended that ketoprofen for dermal use be exempt from the conditions of scheduling.

The Committee concurred with the evaluation report of the applicant's submission. The Committee accepted that the product's indication is suitable for self-identification and self-treatment without professional advice, and that the safety profile indicated there would not be any significant risk to consumers. The Committee acknowledged that interactions with other drugs, particularly anticoagulants such as warfarin, may be significant with ketoprofen when administered orally, however the consensus amongst members was that as plasma levels following dermal administration of ketoprofen are low, interactions are unlikely to be clinically significant.

The Committee recognised that ketoprofen when administered topically has a very low systemic bioavailability, a very low to absent abuse potential and few adverse events from considerable post-marketing experience. Further the lack of significant adverse events following the descheduling of similar topical NSAID supported the Committee view that exempting ketoprofen would not lead to significant problems.

A jurisdictional member highlighted that when similar topical NSAID products were made exempt from scheduling, inappropriate S2 labelled products was found in supermarkets, up to a year following the date of effect of the exemption. The Committee strongly supported the position that only appropriately labelled product and not S2 labelled product should be available to the public in unrestricted outlets. Furthermore any advertising of the product should also be appropriately labelled. Jurisdictional members indicated the situation would be monitored.

DECISION 2003/37 - 27

The Committee agreed to exempt ketoprofen in preparations for dermal use based on:

- the indications are for the minor ailments or symptoms capable of easy recognition, self treatment and monitoring by the consumer and does not require medical diagnosis or management;
- it is considered safe for use without the need for pharmacist advice or counselling;
- its acceptable safety profile with considerable local post-marketing experience; and
- it has very low to absent abuse potential and inappropriate use is unlikely to result in any systemic adverse events.

Schedule 2 – Amendment

KETOPROFEN – delete entry.

Schedule 4 – Amendment

KETOPROFEN – amend entry to read:

KETOPROFEN **except**:

(a) in preparations for dermal use; or

(b) when included in Schedule 3.

14.1.3 DEXTROMETHORPHAN

PURPOSE

The Committee considered an application seeking to reschedule sustained release (SR) liquid preparations containing 0.6% or less of dextromethorphan with a recommended dose not exceeding 60 mg, from Schedule 4 to Schedule 2.

BACKGROUND

The Schedule Review Panel reviewed the scheduling of opiates and other substances in Schedule 2 in 1986 to limit the amount of dextromethorphan per dose unit in divided preparations, the percentage of the active ingredient in divided preparations and the maximum recommended dosage of both divided and undivided preparations. Accordingly, the February 1987 Meeting adopted in Schedule 2 a dose limit of 30 mg or less dextromethorphan for both, divided preparations containing 30 mg or less dextromethorphan per dose unit and undivided preparations containing 0.3% or less dextromethorphan, when compounded with one or more therapeutically active substances.

The November 1997 NDPSC Meeting agreed to include single-active undivided preparations containing 0.3% or less of dextromethorphan in Schedule 3, when labelled with a recommended dose not exceeding 30 mg of dextromethorphan, in packs containing not more than 600 mg of dextromethorphan. However, the February 1998 Meeting set aside this decision and amended the Schedule 2 entry to allow the same controls for single-active and compounded preparations, while retaining the existing limits. The Committee was of the view that it was unlikely that registration of single-active products as Schedule 3 medicines would be sought by sponsors, as a Schedule 2 availability would be preferred. This scheduling had remained current to this time.

A proposal to reschedule a SR liquid formulation from S4 to S2 was considered at the November 1998 meeting. However, the Committee did not support the proposal on the grounds that there were no products of this type registered on the ARTG therefore, no product evaluation was undertaken by the TGA in the past to allow a risk assessment of potential public health issues. The sponsor was subsequently advised that it would be more appropriate for the NDPSC to consider the scheduling of dextromethorphan SR formulation following the approval of the product for registration by the TGA.

CONSIDERATION

XXXXXXXXX proposed to reschedule from S4 to S2, a SR liquid preparation XXXXXXXXX. This product was designed to deliver dextromethorphan over an extended period of time, which allowed dosing on a 12-hourly basis. The proposed product XXXXXXXXX.

DISCUSSION

The Committee noted that XXXXXXXXX raised the following points in support of its proposal:

- The SR formulation offered additional choice and convenience to the self-treating patient with the advantages of less frequent dosing for added convenience and greater coverage of cough relief to help increase compliance therefore optimise the effect of the drug.
- The maximum daily dose for the SR product was the same as IR preparations XXXXXXXXX, and was within the recommended dosage guidelines for dextromethorphan for the treatment of non-productive cough. The higher concentration of dextromethorphan HBr in the SR liquid formulation XXXXXXXXX allowed the product XXXXXXXXX adult dose normally associated with liquid cough/cold preparations.
- The pharmacological/toxicological profile of dextromethorphan was well understood and the drug was recognised as a safe and effective antitussive agent. Adverse effects associated with dextromethorphan were rare, although nausea and/or GI disturbances, neurological and cardiovascular disturbances, slight drowsiness and dizziness were noted to occur. The drug produced no significant analgesic and addictive effects and produced negligible CNS depression although excitation, confusion, and respiratory depression could occur after an overdose.
- Dextromethorphan was widely available worldwide without prescription for over 40 years and its safety profile was well established in the OTC environment. XXXXXXXXX marketed an undivided SR liquid dextromethorphan preparation in Canada since August 1997, and post-marketing data suggested that there was no difference in the safety profile between IR and SR formulations. In addition, no unexpected adverse events were reported with the SR product.
- Cough is a very common symptom experienced by consumers, usually in association with colds, and consumers are capable of recognising and treating this symptom without pharmacist intervention. The proposed product had the same indication as existing OTC IR products. Dextromethorphan was not recommended for chronic, recurrent cough therapy and labelling for the SR product would clearly advise consumers to discontinue using the product should coughing persist.
- Although dextromethorphan is the dextro-isomer of levorphanol, no chiral conversion of dextromethorphan to opioid levomethorphan occured in humans. All experimental

and clinical data indicated that the dependence risk potential for dextromethorphan was low. Allowing SR dextromethorphan in S2 would not increase the availability of the drug and there was no evidence to suggest that its availability would pose a greater risk than currently available dextromethorphan products, from an abuse perspective.

- The primary target for abuse was generally the tablet or powder dosage form of dextromethorphan as cough syrups were bulkier, and contained ingredients that may cause vomiting when taken in large enough quantities. The liquid preparations were also less concentrated than tablets (15 mg/teaspoon of syrup vs. 30 mg/tablet) and not all the dextromethorphan was immediately bio-available therefore, a greater quantity of the preparation (at a greater cost) needs to be taken by the abuser to get the desired effect.
- XXXXXXXXX believed that the proposed inclusion of dextromethorphan SR liquid preparations in S2 should not lead to additional safety or abuse implications for use by the general public beyond those already experienced with currently available IR preparations.

The Committee noted the evaluation report highlighted the following points:

- The proposed slow release (SR) liquid product was yet to be evaluated by the TGA. The submission contained inadequate information about the proposed product and a proper assessment of the merits of the argument for rescheduling may be possible following the evaluation of the registration submission.
- The indication of both SR and IR formulation were the same therefore it may be appropriate to allow both formulations in S2.
- Dextromethorphan had a moderate potential for abuse and psychological dependence had been reported.
- The recommended total daily dose of the proposed SR product would have twice the concentration (60mg/10mls) of the current IR liquid product. This could pose a greater risk for harm following inappropriate use, particularly accidental ingestion by children. The higher concentration may also increase its attractiveness to dextromethorphan abusers.
- A reasonable argument was made to suggest that, when used as directed, the SR formulation would not provide an increased risk to consumers compared with currently available IR formulations. However, the argument regarding its safety following inappropriate use was less convincing.
- No detail was provided concerning the proposed packaging and labelling, e.g. requirement for CRC.
- There was no marketing experience within Australia for the new SR preparation (not yet approved) and limited experience overseas (only marketed in Canada). The spontaneous reporting rate of adverse events was low and post-marketing surveillance suggested that the preparation was safe in over the counter use however, there were

some interesting and unexplained differences in the pattern of adverse effects with the SR formulation compared to the IR.

- The public health argument for the need for this product was not outweighed at this stage by the concerns on the potential for misuse and harm from accidental ingestion.
- The evaluator recommended that existing scheduling for dextromethorphan be retained in terms of the strength and dosage allowed in Schedule 2, and further consideration of the proposal could be deferred until more detail was available concerning the proposed product.

The Committee noted the following pre-meeting comments were received:

- XXXXXXXXX supported the proposal to modify the Schedule 2 entry to allow for undivided preparations with a recommended dose of greater than 30 mg of dextromethorphan in a sustained release format.
- XXXXXXXXX was a sponsor of products containing dextromethorphan and indicated its interest in any decisions taken affecting the scheduling of this substance.

Members noted the reports of serious dextromethorphan poisoning in children, aged 1 to 4 years, involving combination dextromethorphan products as well as sustained-release preparations at doses ranging from 5 to 21 mg/kg dextromethorphan (75 mg to 315 mg dextromethorphan for a 15-kg child). [*Vet Human Toxicol 30 (4) August 1988]*. The Journal of Toxicology (38, 2000) reported that moderate to severe symptoms of dextromethorphan poisoning could occur at doses of 10.3-24.2 mg/kg (14-33 mg/kg dextromethorphan hydrobromide or 700-1650 mg for a 50-kg individual). Severe symptoms cited included seizures, coma and multiple seizures. A member also pointed out that the USP Drug Information monograph indicated that toxic psychosis was reported after ingestion of as little as 300mg of dextromethorphan (50mls of SR liquid).

The Committee was informed that several PICs around Australia advised that cases of overdose relating to dextromethorphan could not be differentiated from cases relating to other cough/cold medication as the active ingredient(s) in implicated products were not recorded. The XXXXXXXXX also advised that it adopted the POISINDEX treatment guideline of referring children who were symptomatic and those who ingested a long-acting dextromethorphan preparation to a healthcare facility for evaluation. The guideline also recommended that children who ingested less than 10 mg/kg of regular dextromethorphan may be managed at home.

The Committee noted that the Adverse Drug Reactions Advisory Committee (ADRAC) report showed a very low incidence of adverse reactions associated with dextromethorphan single-active preparations in Australia. Members also noted that the evaluator indicated that there were no safety concerns associated with the SR products based on the spontaneous reporting rate of adverse events and overseas post-marketing surveillance which also supported safety in over the counter use. However, the evaluator noted that there were unexplained differences in the pattern of adverse effects with the SR formulation compared to the IR, i.e. SR causing relatively fewer cardiovascular

effects and skin reactions but relatively more nervous system effects, particularly insomnia and nervousness.

A member highlighted that the sponsor's submission did not address the potential for children ingesting larger amounts of dextromethorphan due to higher concentration of active in the SR preparation and that there was a strong case for requiring child-resistant closures (CRC) on such products. The Committee agreed that there may be a case for requiring CRC on SR dextromethorphan products, however this issue would be dealt with at product registration. In addition, the Committee noted that PICs appeared to already have an existing management protocol in place for cases of dextromethorphan overdose particularly for children, which took into account a modified approach for SR preparations.

A member raised a concern that the SR formulation could become the preferred product for abuse, as a smaller volume of the product would be required to achieve the desired effects. The Committee noted that the adoption of a pack size limit of 600 mg dextromethorphan in S2, a decision made under agenda item 16.1 of this meeting, should ensure that SR products would not have an increased potential for abuse in comparison to existing IR products.

A member proposed to replace the limit on the recommended dosage in S2 with a limit on the total daily dosage of 120 mg dextromethorphan, in addition to the new pack size limit of 600 mg dextromethorphan. The member stated that this should help minimise the potential for inappropriate use or accidental overdose by keeping the total daily intake uniform, irrespective of the type of formulation.

OUTCOME

The Committee agreed to foreshadow the decision to replace the existing S2 limit on the recommended dosage with a total daily dose limit of 120 mg dextromethorphan for all preparations, in order to minimise the potential for inappropriate use or accidental overdosage. In addition, the Committee was of the view that this approach should also ensure that the SR format would not pose a greater risk compared to the traditional IR formulation by ensuring a uniform total daily dose for both formulations.

FORESHADOWED (for consideration at the June 2003 meeting)

Schedule 2 - amendment

DEXTROMETHORPHAN - amend entry to read:

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

DECISION 2003/37 - 28

The Committee agreed that it would be appropriate to include all modified release undivided preparations containing 0.6 per cent or less of dextromethorphan with a recommended daily dose of 120mg or less of dextromethorphan in Schedule 2. This decision was based on the following:

- The indication and recommended daily dosage of the sustained-release (SR) format was the same as the immediate-release (IR) formulation already in Schedule 2. The Committee agreed that there was adequate evidence to suggest the safety of the SR formulation as S2 medicine, based on the Adverse Drug Reactions Advisory Committee (ADRAC) report and overseas post-marketing surveillance data in OTC use.
- The Committee was of the view that limiting the pack size (decision under agenda item 16.1) to 600 mg dextromethorphan should address the problem associated with the drug's potential for abuse. It was agreed that maintaining a pack size limit on all preparations in S2 should ensure that the SR formulation would not become a preferred product for abuse or diversion as a consequence of the higher dextromethorphan concentration in this formulation.
- The recommended total daily dose of 120 mg dextromethorphan for undivided, modified release preparations was consistent with the recommended daily dose of currently available IR preparations in S2. Members agreed that specifying a uniform maximum daily dose limit for both SR undivided preparations which was consistent with that of IR preparations in Schedule 2 should address the potential for accidental overdose from inappropriate dosing. Furthermore, this approach should also ensure that there were no additional safety concerns arising from inappropriate use due to the modified dosing regimen and modified release format of the SR formulation.

Schedule 2 - Amendment

DEXTROMETHORPHAN - amend entry to read:

DEXTROMETHORPHAN when supplied in a pack containing 600mg or less of dextromethorphan:

(a) in divided preparations containing 30mg or less of dextromethorphan per dosage unit and with a recommended dose of 30mg or less of dextromethorphan; or

(b) in undivided preparations containing 0.6 per cent or less of dextromethorphan with a recommended daily dose of 120mg or less of dextromethorphan.

14.1.4 ORLISTAT

PURPOSE

The Committee considered the scheduling of orlistat.

BACKGROUND

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

XXXXXXXXX markets XXXXXXXXX containing 120mg 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. A submission submitted by XXXXXXXXX to reschedule orlistat from S4 to S3 was considered at the June 2002 NDPSC meeting, however the Committee agreed that the current S4 scheduling for orlistat remained appropriate.

DISCUSSION

The XXXXXXXXX declared a potential conflict of interest for this item. The Member had been involved in negotiations on behalf of XXXXXXXXX for a "fee-for-service" agreement for orlistat management and counselling. The Member left the room whilst the Committee discussed this declaration. The Committee considered that this activity was not a conflict of interest and agreed that the Member could continue to participate with voting rights.

The applicant highlighted the following points in support of its submission:

- XXXXXXXXX has been used extensively for over 5 years and has been registered in Australia since May 2000. It has an estimated worldwide patient exposure of XXXXXXXXX patient treatments. The incidence of serious adverse events is very low (0.009% patient treatments) and equal to placebo.
- Obesity puts millions of lives at risk and has been identified as a major risk factor in the development of non-insulin dependent diabetes, impaired glucose tolerance, hyperinsulinaemia, hyperlipidaemia and hypertension. Moderate weight loss improves morbidity and mortality.
- Orlistat has consistently achieved more weight loss compared with placebo as well as maintaining weight loss and preventing weight gain. Impaired glucose tolerance and hyperlipidaemia were also improved. There is minimal risk of masking serious disease by the use of orlistat.

- Effective sustained weight loss in obese patients will lead to decreased health care costs to the community. The Australian Institute of Health and Welfare in 1989-90 estimated the health care costs of obesity related diseases at 1.3 billion dollars. The appropriate use of orlistat as an S3 medicine will result in improved access for overweight patients and will help reverse the current trend of the increasing prevalence of obesity in Australia.
- The indication for XXXXXXXXX meets the criteria for an S3 medicine. Obesity and overweight are easily diagnosed by the pharmacist and confirmed using the patients height and weight and a BMI index chart or BMI calculator.
- Close medical monitoring is not required as orlistat is safe, weight loss is gradual, supply of orlistat as an S3 agent will be regulated by the pharmacist, drug interactions are minimal and side effects are mostly mild, transient and self-limiting and are related to the mechanism of action.
- Long term safety data is available and confirms that orlistat is safe. The most common adverse events occur when excessive fat is ingested along with orlistat and decrease with time as the patient implements the practice of reducing fat intake in their diet. Due to the localised mode of action, side effects are generally avoidable. In clinical trails, very commonly observed side effects were generally mild and transient and occurred early in treatment (within 3 months) and most patients experienced only one episode. Only 3% of patients experienced more than 2 episodes of any one adverse event.
- Drug interactions with orlistat are rare. Reported drug interactions include cyclosporin, oral hypoglycaemics, warfarin and fat-soluble vitamins which can be identified by the pharmacist and the patient can be referred to their GP if needed. Orlistat does not interact with common agents such as alcohol, oral contraceptives, nifedipine, phenytoin, digoxin and pravastatin.
- The potential for misuse of orlistat is low because the use of orlistat in the presence of a high dietary fat intake will lead to unacceptable GI symptoms. In the case of a patient with bulimia, the pharmacist would recognise that the presenting person had a normal to low BMI and would therefore not supply the product. Orlistat has no clinical effect in the absence of food, is only minutely absorbed and has no systemic effect so could not be misused by anorexics.
- Contraindications are listed for chronic pancreatitis and pancreatic enzyme deficiency and chronic malabsorption syndrome. These patients are unlikely to present to a pharmacist for treatment. If they did use orlistat, the drug would be ineffective due to reduced levels of intestinal lipase due to the underlying condition. Orlistat inhibits lipase activity and is not active in the absence of lipase.
- Obese patients should be assessed for co-morbid conditions, however this assessment should not be conditional to treatment for weight reduction. Weight reduction itself will benefit or prevent co-morbid conditions such as hypertension, type 2 diabetes mellitus and hyperlipidaemia. The potential for adverse sequelae associated with co-morbid conditions is reduced with effective weight reduction. The pharmacist has a

role to refer all patients to their GP for regular health checks, regardless of their weight status.

- The pharmacist will encourage the use of diet and exercise and other lifestyle changes as first-line therapy for weight loss. The availability of XXXXXXXXX at pharmacy level will increase patient-pharmacist contact and will allow early professional intervention rather than unsupervised use of the unproven pharmacologic agents that are currently used.
- A four year XXXXXXXXX study confirmed earlier efficacy findings that patients on a controlled diet and exercise regimen will loose weight. The study also confirmed that the addition of XXXXXXXXX will double the weight loss over a four year period.
- XXXXXXXXX treatment focuses on lifestyle changes as integral to successful weight loss. It is not promoted in the absence of lifestyle changes. The XXXXXXXXX weight management program is an integral part of successful and sustained weight loss. This program is available to patients at no additional cost. The program reinforces the need for lifestyle changes and has been shown to significantly improve patient outcomes and increase patient satisfaction with treatment. It is considered by pharmacists as the gold standard of patient support programs.
- The XXXXXXXXX Weight Management Program provides substantial dietary and exercise advice. Dieticians, exercise physiologists and nutritionists are available to speak to the patient as often as required. The patient is also free to seek advice from their own dietician and exercise physiologists outside the program. The need for psychological counselling can be discussed and the pharmacist can refer them back to their GP if necessary. The patient will return at least monthly to purchase the product which provides a good opportunity to review treatment concordance, weight loss progress and discuss lifestyle changes.
- Orlistat meets all S3 classification criteria: low potential for abuse, low potential for harm from inappropriate use, low incidence of severe adverse effects, side effects unlikely to require medical intervention, few drug interactions, medium to wide therapeutic index and few contraindications.
- Orlistat is not recommended during pregnancy or lactation and as such, pharmacists will not supply XXXXXXXXX to pregnant or breastfeeding women. Orlistat has been given a pregnancy classification of B1 (drugs which have been taken by only a limited number of pregnant women and women of child-bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed). In contrast, NSAID's have a pregnancy classification of C and nicotine replacement therapy products have a pregnancy classification of D, both of which are available at the pharmacy level.

The Committee noted the following issues from the evaluation report:

- To optimise the successful treatment of obesity, pharmacotherapy should be initiated only after dietary modification, exercise and behavioural therapy have been formally

and rigorously undertaken for at least several months. Non-pharmacologic therapies can be successful in up to 50% of patients in controlled clinical trials.

- The wider availability of orlistat as an S3 product will impart the wrong public health message that freer availability of this agent suggests earlier pharmacotherapy is appropriate, even though exercise, dietary and behavioural approaches by relevant experts, undertaken for at least several months, may alone be efficacious.
- The 4-year placebo controlled study submitted by the sponsor showed a reduction in the development of type II diabetes in those patients with impaired glucose tolerance at baseline. This change may occur with weight loss alone through non-pharmacologic measures. Furthermore, there was a steady decrease in attributable weight loss over the 4-year clinical trial period. That is, there was evidence of decreasing efficacy with time.
- There was no quantitative data provided on the falls in levels of fat soluble vitamins seen in the clinical trials. Furthermore, it was stated that patients may have received vitamin supplementation therapy during the study, however relative percentages of patients receiving supplementation in the orlistat vs placebo group were not provided.
- Despite large international sales over 5 years, there has been as yet no demonstrable public health benefits with orlistat.
- The sponsor argues that the pharmacist providing S3 orlistat is able to refer the patient to their doctor for co-morbidity screening, however screening must occur in all patients with BMI's above 27 and would routinely occur if the patient presented at their doctor for treatment of weight loss.
- The evaluator supports the retention of orlistat in S4 due to the complexity and staged approached to obesity management which is the current accepted "gold standard" of care.

Pre-meeting submissions were received from the following:

- XXXXXXXXX supported the rescheduling of orlistat to S3 as it meets the safety criteria for an S3 medicine according to the NDPSC guidelines. It is substantially safe in use, has a low incidence of severe adverse effects or side effects which are likely to require medical intervention and the condition is capable of being monitored by the consumer with assistance from a pharmacist. Community pharmacists have a vital role in assisting customers to seek appropriate treatment which includes referral to a medical practitioner. The inclusion of orlistat in Appendix H was not supported as it may encourage customers to seek therapeutic intervention as a first-line treatment without consultation with a health care professional.
- XXXXXXXXX supported the inclusion of orlistat in Schedule 3 of the SUSDP, but did not support its inclusion in Appendix H. The submission highlighted that pharmacists are well qualified to provide support and monitoring for people taking orlistat which may produce considerable health benefits for individuals at risk of cardiovascular disease and type II diabetes. It also highlighted that the advertising of

such a product may induce those with eating disorders associated with anorexia and bulimia to use orlistat inappropriately.

- XXXXXXXXX did not support the rescheduling of orlistat prior to the June 2002 meeting. It was concerned about the limited post-marketing experience and the appropriateness of the use of orlistat as a non-prescription medicine. XXXXXXXXX highlighted the issues associated with the use of orlistat in patients with endocrine disorders, fat-soluble vitamins and calcium supplementation, and concomitant drug administration. XXXXXXXXX recommended the rescheduling of orlistat be deferred until more comprehensive, rigorous and up-to-date information about the product is available to pharmacists. In their pre-February 2003 submission, XXXXXXXXX stated that their concerns have largely been addressed and therefore now support the inclusion of orlistat in Schedule 3, but do not support the inclusion of orlistat in Appendix H.

The Committee noted that a number of testimonials in favour of S3 availability for orlistat were received from individuals, pharmacists and medical practitioners.

The XXXXXXXXX did not support the rescheduling of orlistat to S3 nor its inclusion in Appendix H. The Member expressed concerns that the S3 availability of orlistat would place an onerous responsibility on pharmacists and as a general rule, pharmacists are not equipped for this level of counselling. Also, long-term counselling would be difficult to sustain as consumers may not stay with one pharmacist, therefore the continuity of care would be disjointed. The Member noted that consumer organisations have been concerned over some of the sponsor's consumer promotional activities while orlistat has been included in S4, as weight management, obesity and weight loss are areas which many consumers are vulnerable to persuasive advertising and promotional activities. The Member felt that rescheduling orlistat was premature at this time and that further evidence of its use and efficacy was needed.

The Committee noted the NHMRC draft report on the National Clinical Guidelines for Weight Control and Obesity Management in Adults (draft report released September 2002 – final report due in August 2003). The report listed a three tiered approach to weight control and obesity management. The first was education which is aimed at overweight or obese individuals, the second was cognitive behaviour change which is aimed at overweight or obese individuals with disordered eating patterns or cognition and the third was surgery or drugs combined with very low energy diets which is aimed at morbidly obese individuals.

The Committee noted the following evidence statement and recommendation in the NHMRC draft report:

<u>Evidence Statement:</u> Orlistat combined with a low-energy, low-fat diet can lead to a weight loss of 8.5kg (6-13kg), or about 8.6%, and improve some co-morbid factors after one to two years of treatment. Two-thirds of this weight loss is the result of diet modification. The safety of prolonged (more than two years) therapeutic use of orlistat has, however, not been demonstrated.

<u>Recommendation:</u> Pharmacotherapy can be a useful adjunct to lifestyle change to induce weight loss in some patients with a BMI greater than 30 and in patients with a BMI greater than 27 with co-morbidities. It is, however, clear that the medication is effective only while it is being taken and, in the absence of long-term (more than two years) data, the long-term risk-benefit ratio of new drugs (such as sibutramine and orlistat) cannot be predicted. Drugs should be used only under careful medical supervision and in the context of a long-term treatment strategy.

Members noted that the NHMRC draft report recommended that medication should be considered only for patients whose health is severely impaired because of their excess weight and who have been unsuccessful losing weight in other ways. The report also highlighted that obesity should be considered and managed as a chronic illness and pharmaceutical treatment may be necessary in carefully selected obese individuals if the health benefits outweigh the potential risks of the treatment. Members strongly supported the view expressed in the draft report that drugs should not be necessary in the treatment of moderately overweight individuals where an increase in physical activity should be sufficient to deal with the problem.

The Committee noted that the findings of the XXXXXXXXX Study quoted in the sponsor's application showed marginal effectiveness and that counselling was included as part of the treatment plan. Given that there was no breakdown of statistical data or full details of the study provided in the sponsor's application, members were unable to determine the frequency at which counselling was given to subjects in the duration of the study.

Members also raised the concern that whilst orlistat may assist weight loss by reducing the absorption of dietary fat, this treatment option would be ineffective for obese patients who have high sugar or high carbohydrate diet.

The Committee identified obesity as being unlike other Schedule 3 indications in that the preferred first-line treatment for such a condition are non-pharmacologic therapies such as dietary and lifestyle changes. Members were of the view that increasing the availability of orlistat could significantly increase the potential for orlistat to be used routinely as a preferred second-line treatment instead of behavioural counselling under the supervision of a medical practitioner, in cases where patients refuse to make the necessary lifestyle changes. The Committee recognised that pharmacologic intervention including treatment with orlistat is appropriate for the treatment of refractory obesity where all non-pharmacologic options available had been attempted without success. Members agreed that pharmacologic intervention should not be routinely used (safety not withstanding) where there was a potential for non-pharmacologic therapies to work successfully on a long term basis. On this basis, the Committee agreed that patients may be unable to determine which treatment option is most appropriate without the advice and on-going monitoring of a medical practitioner.

Notwithstanding the intervention of a pharmacist at the point of sale, some members still expressed concern regarding the potential for abuse by individuals who have an eating

disorder and currently use laxatives to reduce weight gain after eating. The sponsor claimed that the undesirable GI effects would deter abuse. These Members noted that if laxatives are currently being used, the GI effects are precisely the effect these individuals are aiming for. Orlistat could be seen as an alternative to laxatives and/or vomiting following a meal which was a major concern for the Committee. This may bring undue pressure on pharmacists to supply orlistat for inappropriate use. Nevertheless, the Committee noted the sponsor's statement that individuals would be screened by pharmacists and that individuals with a BMI below 27 would not be given access to orlistat.

Members acknowledged that whilst the sponsor provided responses to some of the Committee's concerns from the June 2002 meeting, members agreed that the application did not provide adequate grounds to support rescheduling of orlistat. In relation to the specific answers provided by the sponsor in response to the Committee's initial concerns raised at the June 2002 meeting, the Committee made the following observations:

- The Committee agreed that based on the mode of action of orlistat, it was likely that the major side effects are mainly gastrointestinal in nature, which are both predictable and manageable. However, the major issue of potential for induction of fat soluble vitamin deficiencies and concomitant metabolic bone disease remains. This issue was not satisfactorily addressed based on the available information from the XXXXXXXXX study and therefore remains unresolved.
- The Committee noted that while it may be possible for pharmacists to refer patients to doctors for pre-screening for co-morbidities prior to supply of orlistat, members felt that this is essential and was best initiated and coordinated by the medical professional, not the pharmacist.
- The Committee acknowledged that some pharmacies have active counselling programs currently running and are successful in providing a high level of counselling to overweight patients. However, members did not believe that all pharmacists are generally equipped or trained to provide the high level of counselling and ongoing support that was employed in the efficacy studies. There is no clinical information showing what commitment the pharmacist needs to make in order for the treatment with XXXXXXXXX to be successful over a period of time, i.e. the level and frequency of counselling necessary for sustainable weight loss.
- The Committee acknowledged that a lack of pharmacy assistant training was not a reason to refuse re-scheduling and had not been used as such. The clarification by the sponsor with regard to training programs was noted by the Committee.

The applicant highlighted the following points in support of its proposal to include orlistat for the treatment of obesity and overweight in Appendix H:

- Obesity is a major public health issue that warrants the active promotion of weight reduction. Active promotion will result in benefits to the individual as well as the Australian community at large.

- Reduction in obesity associated disorders such as cardiovascular disease, type 2 diabetes and certain cancers will reduce mortality, morbidity, health care costs and improve quality of life.
- Consumers benefit from the ability to make informed choices about their own healthcare. Awareness of treatment options may prompt consumers to act on conditions that are difficult to treat, for example obesity. The advertising of XXXXXXXXX has the potential to impact significantly on the health of Australians by prompting those individuals in need of weight loss to consult a health professional.
- Realistic and balanced representation of their condition and possible treatments is needed for consumers to take the correct action, and this is ensured by requirements for advertisers of therapeutic goods to adhere to the TGAC as well as state and commonwealth legislation.
- The pharmacist will be able to offer appropriate advice and treatment of weight loss, and encourage the patient to see their doctor so that other associated illness may be identified, and receive appropriate care and treatment.

The evaluation report of the proposal to include orlistat for the treatment of obesity and overweight in Appendix H stated that as the rescheduling of orlistat to S3 was not supported by the evaluator, the inclusion of orlistat in Appendix H was also not supported.

The Committee noted the sponsor's argument that the advertising of XXXXXXXXX would not lead to inappropriate patterns of medication use. However, the sponsor only commented on the lack of availability of the medicine to a bulimic or anorexic person - pharmacists would not supply the medication to individuals who did not meet the BMI requirements - not the possibility that these types of people would actively seek out this medication once advertised placing undue pressure on pharmacists to supply orlistat.

In support of the inclusion of orlistat in Appendix H, the sponsor cited public health benefits such as a reduction in the number of obese individuals and a reduction in associated health costs. Whilst successful and long term weight loss in obese patients is desirable and has undoubted health benefits for the community, the Committee remained unconvinced that advertising of orlistat would not increase the potential for inappropriate use of the substance by vulnerable individuals.

The Committee raised concerns that advertising of orlistat could significantly impact on the public's acceptance of lifestyle changes as a first option and promote unreasonable expectations of the effectiveness of pharmacotherapy in weight loss. This may in turn produce a negative impact on public health as substitution of effective forms of first-line therapies with orlistat may decrease the overall success in controlling obesity.

OUTCOME

The Committee's concerns raised at the June 2002 meeting had, in the main, not been dispelled by the sponsor's latest submission. The Committee agreed that retention of orlistat in Schedule 4 remained appropriate due to the following:

- Obesity was not a short-term, self-limiting disease - rather there was a need for long term intervention to successfully manage obesity. Promotion of pharmacotherapy may lead to unreasonable expectations of effectiveness in what may be vulnerable target groups. A multi-disciplinary approach was required to successfully treat obesity (GP, dietician and a counsellor/psychologist). 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 in public health terms.
- There was no OTC experience with orlistat anywhere in the world. Therapeutic weight loss products should only be used as a last option. Lifestyle changes such as a controlled diet and regular exercise should always be attempted first. The efficacy of orlistat was based on highly controlled clinical studies and there was no adequate evidence to demonstrate that orlistat was efficacious in sustaining long-term weight loss in the absence of dietary restraint, therefore reinforcing the point that lifestyle changes should be encouraged as a first-line treatment.
- The need for dietary supplementation with fat-soluble vitamins and the influence of orlistat treatment on nutritional status remains unresolved.
- Pharmacists in the traditional pharmacy setting were not equipped to screen for the associated conditions (diabetes etc) or the potential adverse effects and were not set up to handle the high level of counselling and on-going support needed for effective utilisation of orlistat in a weight loss regimen.

The Committee agreed 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.

14.1.5 NABILONE

PURPOSE

The Committee considered the scheduling of nabilone.

BACKGROUND

Nabilone is a synthetic cannabinoid used as an anti-emetic in the treatment of nausea and vomiting caused by chemotherapy primarily for patients who are not responsive to conventional anti-emetic treatments. Nabilone was included in Schedule 8 in May 1984 because of its class (synthetic cannabinoid) to ensure it was effectively controlled following general marketing approval by ADEC for 1 and 2 mg capsules. The approved indication was "for the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer". The recommended dosage was 1 to 2 mg bd with

a maximum dose of 5mg daily. The product appears not the have been marketed in Australia.

Nabilone has been marketed in the UK since 1983 as a "hospital only" treatment and has been recently reclassified to "prescription only" medicine in April 2002. Nabilone is now available in the UK in hospitals and specialist clinics and via a prescription from an appropriate specialist such as a palliative care specialist or an oncologist.

Patients in Australia can access nabilone through the TGA's Special Access Scheme (SAS).

DISCUSSION

XXXXXXXXX submitted an application seeking to reschedule nabilone from S8 to S4.

The applicant highlighted the following points in support of its proposed rescheduling:

- More and more cancer treatments are being modified to encourage home-based treatments and community care of cancer patients. Significant advantages would be gained by making nabilone available as a community-based treatment where it will be available in hospitals or on prescription by specialist physicians. The risk to benefit ratio of this approach is acceptable given its safety record in hospital use and reflects a trend of closer supervision of cancer patients in the community.

- Enabling less traumatic chemotherapy with General Practitioner (GP) supervision of symptoms is a powerful way of destigmatising cancer treatment.

- By rescheduling nabilone to S4, it will become much easier to store and supply due to less restriction and paperwork which will in turn reduce costs and make it cheaper for the patient.

- Nabilone is not listed in Schedule I or II of the WHO Single Convention on narcotic Drugs (INCB – yellow list), nor is it listed in Schedule II or III of the WHO Convention on Psychotropic Substances (INCB – green list).

- Nabilone is not likely to present a substantial risk of abuse, dependence or misuse for illegal purposes. Although, as a cannabinoid, it has the potential for abuse, it would only be used on prescription and under restrictive circumstances for a short time for patients who are not responsive to conventional anti-emetic treatments.

The Committee noted the following from the evaluation report:

- The clinical expert report and literature survey of clinical trials provided by the applicant suggested that nabilone is superior to prochlorperazine in its anti-emetic activity although it has high degrees of drowsiness, vertigo, "highs" and dry mouth compared with prochlorperazine.

- Nabilone, like marijuana, acts on the CBI receptor, which is present only on central and peripheral neurons and thus has habituation potential, although it appears to have less habituation potential than THC. Euphoria is seen as a side effect at therapeutic doses of nabilone, however not to the same degree as delta-THC given by similar route.

- The evaluator's recommendation that the rescheduling of nabilone from S8 to S4 be withheld until the clinical trial dataset can be evaluated with the registration submission to the TGA. Of particular concern are its benefit to risk in terms of antiemesis vs adverse event profile and its potential for habituation and misuse.

An internet search did not yield significant reports of abuse or overdose of nabilone and there was no evidence of promotion of nabilone as a substance of abuse. The Committee remained concerned however at nabilone's abuse potential and noted the lack of data on this issue.

The Committee noted, as a comparison, the current status of dronabinol - a delta-9-THC derived cannabinoid used for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments and for the treatment of anorexia associated with weight loss patients with AIDS. Dronabinol is currently included in Schedule II in the list of psychotropic drugs (the green list). The World Health Organisation (WHO) Expert Committee on Drug Dependence had recommended dronabinol to be rescheduled from Schedule II to Schedule IV. If adopted, this rescheduling would mean the relaxation of control with respect to the import and export documentation requirements and the level of detail and frequency of statistical reporting. Australia provides the same level of reports for Schedule III and IV substances as Schedule II substances on a voluntary basis. Dronabinol is currently included in Schedule 8 of the SUSDP while all other THC substances are included in Schedule 9. The Committee has previously noted that nabilone was not an analogue of THC.

The Committee acknowledged that if nabilone was rescheduled to Schedule 4, the storage and record keeping requirements would be less onerous for the wholesaler and the pharmacist. However, the Members noted that there would be no significant differences in terms of the access of nabilone for patients, either as an S8 or as an S4 medicine.

The Committee concurred with the evaluator's opinion that the consideration of the rescheduling of nabilone should be deferred until the clinical trial dataset has been evaluated as part of a registration application.

A Member noted that cancer patients would be likely to be taking other Schedule 8 medicines as part of their treatment regime and as such, the current Schedule 8 classification would not unfairly disadvantage these patients.

OUTCOME

The Committee agreed that the inclusion of nabilone in Schedule 8 remained appropriate at this time as the application for rescheduling did not provide adequate evidence on abuse potential and did not provide a clear proposed pattern of use. The Committee also noted that retention of nabilone in Schedule 8 rather than Schedule 4 of the SUSDP did not disadvantage patients in terms of access and had no impact with regard to the Special Access Scheme.

14.1.6 BECLOMETHASONE

PURPOSE

The Committee considered an application seeking rescheduling of beclomethasone intranasal preparations.

BACKGROUND

Beclomethasone is a corticosteroid with mainly glucocorticoid activity. It is used as a nasal spray in the prophylaxis and treatment of seasonal and perennial allergic rhinitis.

XXXXXXXXX markets XXXXXXXXX containing 50 micrograms of beclomethasone dipropionate per spray for the short-term (3-6 months) prophylaxis or treatment of seasonal allergic rhinitis and perennial rhinitis in adults and children aged 12 years and over.

Beclomethasone was listed as Schedule 4 (S4) in 1991. At the 1998 NDPSC meeting it was rescheduled to Schedule 3 (S3) for the treatment of seasonal allergic rhinitis on the basis of Trans-Tasman scheduling harmonisation with New Zealand. The S3 entry for beclomethasone was extended to include perennial allergic rhinitis at the November 2001 meeting.

DISCUSSION

The Committee noted the following arguments were raised by XXXXXXXXX application to reschedule intranasal beclomethasone dipropionate for the prevention or treatment of allergic rhinitis from S3 to Schedule 2 (S2):

- Used correctly, intranasal corticosteroid sprays control symptoms more completely than antihistamine tablets, providing consumers with a superior treatment option and promoting the quality use of medicines.

- There is extensive experience with the use of beclomethasone dipropionate in the treatment of allergic rhinitis and the data demonstrates intranasal beclomethasone to be safe with minimal risk of systemic side effects.

- The labelling of XXXXXXXXX will be redesigned to enhance readability and provide adequate information for use.

- The product meets the NDPSC Guidelines for S2 listing.

- Intranasal corticosteroids are effective when used on an as needed basis.

- The cost-effectiveness considerations favour intranasal corticosteroids over antihistamines.

- The application does not propose to extend the period of usage beyond the currently approved maximum of 6 months for allergic rhinitis.

The Committee noted from the evaluation report of the applicant's submission :

- The extensive local and overseas experience with intranasal beclomethasone used for the treatment of allergic rhinitis demonstrated it's efficacious for this condition. There appears to be minimal local or systemic risk based on substantial post-marketing data.

- Allergic rhinitis meets the NDPSC guidelines for listing in S2, as it does not require ongoing or close medical diagnosis or management. It can be easily recognised by the consumer and is amenable to self-monitoring by the consumer, with advice and counselling if necessary. It is also unlikely to mask a more serious underlying disease.

- The draft label for XXXXXXXXX is intended to enhance the readability and assimilation of information, providing adequate information for use.

- The evaluator could not differentiate pharmacist only medicine, pharmacy medicine and general sales from the substantial overseas safety profiles with OTC use of intranasal beclomethasone.

- The evaluator recommended the rescheduling of beclomethasone to S2.

The Committee noted the pre-meeting submission from XXXXXXXXX opposing the rescheduling of beclomethasone to Schedule 2 due to its unfavourable pharmacokinetic profile. The argument presented was beclomethasone has a relatively high bioavailability compared with other intranasal corticosteroids such as fluticasone and mometasone and can therefore be delivered into the circulation and exert systemic effects. XXXXXXXXX proposed the additional supervision of a pharmacist was still warranted due to the potential of systemic exposure with intranasal beclomethasone dipropionate.

The Committee was not aware of any periodic safety data specifically comparing pharmacist only medicine, pharmacy medicine and general sales with OTC use of intranasal beclomethasone. The Committee noted that beclomethasone dipropionate aqueous nasal spray was descheduled to general sales classification in the UK, which may produce information relevant to resolving this issue. Further the Committee

considered it appropriate to ask ADRAC to keep a prospective watch on adverse events associated with the treatment of children younger than 12 years old.

A member was concerned that repeated use of the product might cause nosebleeds and also the possible long-term systemic effects retarding growth rates of children. The Committee noted the proposed product label and Consumer Medicine Information (CMI) incorporate a specific warning statement concerning nosebleeds. There was also some data for children 6-9 years old with growth retardation but insufficient data for children 10 years old and over to draw any valid conclusion in relation to use in children under 12 years old. Further, the Committee considered the theoretical argument of bioavailability raised in pre-meeting comment was not supported with evidence of the long-term clinical effects.

The Committee noted the proposed label was performance based for clarity. The company's application included a CMI although this is not required for a S2 product. The Committee also noted the regulation of advertising this product as an S2 therapeutic good would be dealt with through the Therapeutic Goods Advertising Code.

The Committee was advised that the XXXXXXXXX had considered a similar application to reschedule beclomethasone. The XXXXXXXXX rejected the application because the periodic safety updates for OTC use of beclomethasone was limited to 18 year olds and above and had not included adequate data on the 12 to 18 year olds age groups. Members noted the data in this application included 12 year olds and above.

The Committee was advised that in Australia there are two products, XXXXXXXXX and XXXXXXXXX which contain two different active ingredients, fluticasone propionate and beclomethasone dipropionate respectively. The Committee considered this close similarity in naming undesirable and agreed this concern be conveyed to TGA Medicines Evaluation Committee (MEC).

A member strongly expressed the view the product should not be used by children under 12 years old except on medical advice and that a statement like "may cause growth retardation in children under 12 years old" should be included in the labelling of all beclomethasone preparations. The Committee thought it proper to raise the matter with the MEC for consideration at registration.

On balance the Committee agreed to reschedule beclomethasone for short-term prevention and treatment of allergic rhinitis to S2 as it was satisfied that the product was substantially safe when used as directed for consumers, provided it is appropriately labelled and used accordingly.

DECISION 2003/37 - 29

The Committee agreed to include beclomethasone for prevention and treatment of allergic rhinitis in adults and children aged 12 years and over in Schedule 2 based on:

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

- Allergic rhinitis does not require medical diagnosis, is readily diagnosed by the consumer, and is unlikely to mask more serious underlying disease;

- Allergic rhinitis is amenable to self-monitoring while pharmacist advice or counselling would be available if necessary;

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

Schedule 2 – New entry

BECLOMETHASONE in aqueous nasal sprays delivering 50 micrograms or less of beclomethasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

Schedule 3 – Amendment

BECLOMETHASONE – delete entry.

Appendix H – Amendment

BECLOMETHASONE – delete entry.

14.1.7 MITRAGYNINE

PURPOSE

The Committee considered the scheduling of mitragynine.

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 also been 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) noted that the leaves were chewed three times to 10 times a day, with stimulant effects occurring after five minutes to 10 minutes.

Animal experiments with mitragynine have shown that it possesses pain threshold-elevating and antitussive properties. Unlike narcotic analgesics, mitragynine has little effect on gastric mobility, is not antagonised by naloxone, has no opiate-like dependence and has only weak respiratory depressant action. Preclinical trials in humans with mitragynine were conducted by XXXXXXXXX in the early 1970s, but apparently revealed some unacceptable acute effects. It has been speculated that a possible reason for this is the different pharmacological profiles of pure mitragynine and the unprocessed leaf, the latter containing several other alkaloids that may modify the effects of the pure drug.

DISCUSSION

The Committee noted that the DSEB had received an inquiry from an Australian resident wishing to import mitragynine. Mitragynine is not currently listed in the Customs (Prohibited Imports) Regulations 1956, therefore its importation does not require an import permit.

The Committee noted that a search of Australian web sites revealed no sites or chat rooms actively promoting or discussing the use of mitragynine. However, a worldwide search revealed some studies on the analgesic properties of mitragynine and possible use in treating heroin addicts. There were no reports of widespread therapeutic use. However, there were at least two Australian web sites marketing the plant *Mitragyna speciosa* (Kratom).

A Member noted that there were many plants that contained hallucinogenic or psychotrophic alkaloids that were not currently scheduled and that mitragynine is not currently listed in any WHO schedule. Also, there was no evidence of abuse in Australia and the need for the Committee to include mitragynine in the SUSDP at this time was questioned.

While it was agreed that there may be a case not to schedule mitragynine at this time, Members were reminded that when a substance is brought to the Committee under these circumstances, that the Committee should act pro-actively, especially when the substance clearly fits the requirements of Schedule 9 and where there is a clear potential for abuse.

It was suggested that the Secretariat contact XXXXXXXXX to see if the company can provide any documentation associated with the XXXXXXXXX mitragynine trial, in particular the unacceptable acute effects.

The Members noted that if the Committee voted to include mitragynine in Schedule 9 at this meeting, there would be no opportunity for any post-meeting comments to be considered as no pre-meeting submissions were received. The Members agreed to

foreshadow the inclusion of mitragynine in Schedule 9 to allow further opportunity for the public to comment on the scheduling action proposed by the Committee.

OUTCOME

The Committee agreed to foreshadow the inclusion of mitragynine in Schedule 9 of the SUSDP due to its pharmacological profile and potential for abuse.

FORESHADOW

Schedule 9 – New entries

MITRAGYNINE.

MITRAGYNA SPECIOSA.

14.2 SUSDP, PART 5

14.2.1 APPENDIX H

14.2.1.1 SODIUM PHOSPHATE

PURPOSE

The Committee considered an application seeking to include oral preparations of sodium phosphate for bowel cleansing in Appendix H of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP).

BACKGROUND

The June 2002 meeting considered an application to include macrogol 3350 and sodium picosulfate for laxative use in Schedule 4, for consistency with sodium phosphate, and list all three substances for bowel cleansing in Appendix H of the SUSDP. The Committee assessed the submitted information to be inadequate on which to base a scheduling decision and agreed to foreshadow for consideration at the October 2002 meeting the inclusion of these substances in Schedule 4 when in preparations for laxative use. In relation to the proposal to include sodium phosphate, sodium picosulfate and macrogol 3350 for use in bowel cleansing in Appendix H, the Committee did not support this change on the basis that the use specified in Schedule 3 - "bowel cleansing" was not appropriate for advertising on the following grounds:

- The Committee noted that no significant case was made in the submission to support the proposal to list sodium phosphate, sodium picosulfate and macrogol 3350 in Appendix H.

- The Committee had previously agreed at the August 2000 meeting in relation to the decision not to include macrogol 3350 in Appendix H that "there appeared to be no public health benefit associated with including macrogol 3350 in Appendix H", a requirement that must be fulfilled under the NCCTG *Guidelines for Brand Advertising of Substances Included in Schedule 3 of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) - November 2000*.

The October 2002 meeting considered the foreshadowed inclusion of macrogol 3350 and sodium picosulfate for laxative use in Schedule 4 but agreed that the unscheduled status of these substances remained appropriate. This decision was made on the basis of information, which supported the conclusion that the unrestricted availability of these substances for laxative use in Australia had not led to reports of serious adverse events. In addition, there was no evidence of misuse.

DISCUSSION

Members were informed that XXXXXXXXX, acting on behalf of XXXXXXXXX, had submitted a further submission dated December 2002 in support of an Appendix H entry for sodium phosphate to permit advertising of the bowel cleansing product XXXXXXXXX.

Members were reminded of the history preceding this application. It was outlined that XXXXXXXXX, through XXXXXXXXX, had been invited to make a new application in relation to the inclusion of sodium phosphate in Appendix H. The Committee agreed that the current submission would be considered as a completely new submission. Members' attention was drawn to the copy of "*Guidelines for Brand Advertising of Substances Included in Schedule 3 of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) - November 2000*" (NCCTG Guidelines) included in the papers.

The Committee noted in the first instance the "**Issues of Process**" raised by the applicant. With regard to the contention that "…it is incorrect to regard these 10 (the NCCTG S3 advertising Guideline criteria) as 'requirements'." as well as the assertion that these "…guidelines are directory, not mandatory.", the Committee was advised that the use of the word "must" in subsections 52E(1) and (2) makes their application mandatory by both the Committee and applicants. The Committee was further informed that it is the applicant's responsibility to provide the necessary information to address the matters set out in NCCTG Guidelines.

In relation to the issue of competition and the application of the Council of Australian Governments (COAG) guidelines in respect of competition, the Committee was advised that its powers under Section 52D(2) of the Act are governed by the objects of the Act in Section 4. Section 4 dictates that safe handling and uniform approach to control the availability and accessibility of poisons in Australia should be the main consideration by the Committee in the exercise of its powers. The Committee agreed that while the COAG guidelines make it clear that any regulation should restrict competition no more

than public benefit requires, this must be considered in light of the objects of the Act. Consequently, the Committee did not accept the assertion of the applicant that "..the Committee must assume that advertising of a S3 medicine will confer a public health benefit unless it can satisfy itself that it will not, and not the reverse.". The Committee concluded that the applicant must demonstrate an actual or potential public health benefit from direct to consumer advertising in accord with the NCCTG Guidelines.

In assessing the application for the inclusion of a bowel cleansing preparation containing sodium phosphate in Appendix H, the Committee has taken into account the arguments presented by the Applicant in its submission dated December 2002. The Applicant's submission was considered by the Committee against the relevant criteria contained in the NCCTG Guidelines.

The Committee proceeded to consider each of the core issues ("**The ten criteria**") contained in the application.

A. Potential Public Health Benefit

The Committee noted that the applicant submitted "….that there are significant **potential** public benefits for XXXXXXXXX to be advertised to the public." and that "It is in the public interest that information of the kind set out in the XXXXXXXXX Consumer Medicine Information (CMI) should be available to people.". The applicant provided argument under three major points: more appropriate use of scarce health resources; a better-informed community and fewer side effects.

It was the Committee's view that bowel cleansing is required not as a treatment for a medical condition but is a necessary pre-condition for certain invasive medical procedures, including colonoscopy, bowel surgery and rectal examination. As such, a patient has already visited the relevant specialist and been advised of the need for this preparation. The selection of the appropriate product to use often had already occurred as part of the broader consultation with the specialist and therefore the Committee did not agree that advertising could lead to any better use of health resources.

Further, the Committee contended that there was a need to take into account and weigh a complex range of factors including the nature and timing of the procedure, the age, physical condition and medical history of the patient, and the appropriate dose form and route of administration for the patient, prior to selecting a bowel cleansing product. The Committee was in complete agreement that these were **NOT** matters appropriately discussed in direct-to-consumer (DTC) advertising, nor were they capable of appropriate assessment by the patient on their own. Accordingly the Committee agreed that the selection of a bowel-cleansing agent required a high level of professional advice and counselling and that it was not appropriate for any level of self-selection on the part of the patient. The Committee noted that this was primarily ensured through inclusion in Schedule 3 while at the same time maximising access without recourse to prescription.

Finally, given the above points, the issue of potential side effects was also one of the many factors for professional consideration prior to the recommendation of a product. The Committee noted that advertising direct to professionals in relation to all of these factors including side effects was permitted for Schedule 3 substances.

B. Inappropriate patterns of medication use.

Members accepted the applicant's contention in relation to their proposed advertising campaign being designed to reinforce all the principles of quality use of medicines.

However, the Committee remained seriously concerned over the inadvertent promotion of misuse. The CMI for the applicant's product, does not state that it may be used for laxative use, however, it does refer to a laxative action in a number of places. Likewise the applicant claimed that a permissible representation in relation to advertising for their product would be to "Promote body's elimination functions.". The Committee agreed that both of these sources of information if widely disseminated and promoted publicly, were easily misinterpreted to mean "laxative use" by those predisposed to abuse laxatives. Considering the proven potential for serious side effects if so abused, the Committee agreed that wide public promotion of such information through advertising was highly undesirable.

C. The wider regulatory system.

The Committee accepted that the applicant would not intentionally breach the Therapeutic Goods Advertising Code or other relevant legislation.

D. Advertising for other than an approved indication.

The Committee accepted that the applicant would only advertise bowel cleansing to consumers and not any other unapproved indication.

E. Responsibility of Pharmacists.

The Committee noted that the proposed advertising would stress the role of pharmacists. The Committee remained concerned that advertising may foster the development of improper expectations regarding the product (that is use as a laxative) in susceptible sectors of the public, leading to undue pressure on pharmacists to supply for uses other than bowel cleansing.

F. Available consumer medicine information.

The Committee noted the availability of CMI and that the possible impact had been discussed under "B" above.

G. Patient Education.

The Committee accepted that patients have a general right to information regarding their medication. However, the provision of product-comparative information to the patient is only important where the patient is actually making the choice of product. The Committee agreed that this had been adequately explored under "A" above. Further the Committee agreed that any specific information regarding use or potential side effects was best discussed by the patient in the context of professional advice and selection of an appropriate product. For these reasons the Committee disagreed with the applicant's contention that there was a place for direct-to-consumer advertising of sodium phosphate for bowel cleansing to supplement the information normally provided by the specialist, the pharmacist and the CMI. In addition, the Committee noted that where the choice of product was predetermined by the medical specialist, there was also the possibility that consumer advertising that suggested there may be some choice of product may in fact lead to greater patient confusion rather than better understanding of the product to be used.

H. Patients managing their own medication

The Committee accepted that patients are willing to accept much more personal responsibility for medication and the treatment of their conditions. However, in this case patients were not involved in treating a medical condition but rather preparing for a medical procedure. It is highly unlikely that any patient would wish to change a professional recommendation in such circumstances and any event the Committee rejected the suggestion that such an outcome was desirable or should be promoted where a specialist had ordered the use of a particular preparation for bowel cleansing.

I. Pharmacists advice.

The Committee accepted that the applicant would include the statement "Your pharmacist's advice is required." in any advertising material as required by the Therapeutic Goods Advertising Code. The Committee also observed that while a pharmacist may advise a patient that a product is available for other uses on prescription where these uses have been approved by the TGA, this would be in the context of the need for intervention by a medical practitioner and the immediate availability of suitable OTC alternatives.

OUTCOME

The Committee rejected the applicant’s proposal to include sodium phosphate in Appendix H of the SUSDP based on the following rationale:

- The applicant had not demonstrated an actual or potential public health benefit arising from the direct-to-consumer advertising of sodium phosphate for bowel cleansing when included in Schedule 3.

- The selection of an appropriate bowel cleansing product requires professional advice and recommendation. This was unlikely to be a matter for consumer choice and therefore inappropriate for direct-to-consumer advertising.
- Direct-to-consumer advertising of sodium phosphate for bowel cleansing also may:
  - inadvertently promote the inappropriate use of such Schedule 3 products as a laxative with potential for serious side effects if misused;
  - place pharmacists under undue pressure to supply such Schedule 3 products for uses other than bowel cleansing; and
  - lead to patient confusion where the product choice was predetermined by a medical specialist.

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

15.1 NEW SUBSTANCES

15.1.1 TADALAFIL

PURPOSE

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

BACKGROUND

Tadalafil is a selective phosphodiesterase (PDE) type 5 inhibitor similar to sildenafil XXXXXXXXX.

The ADEC August 2002 meeting recommended the approval of XXXXXXXXX containing 10mg and 20mg tadalafil for the treatment of erectile dysfunction in adult males. XXXXXXXXX is not indicated for use by women.

DISCUSSION

The Committee noted that tadalafil was classified as 'prescription medicine' in New Zealand.

DECISION 2003/37 - 30

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

Schedule 4 - New entry

TADALAFIL.

15.1.2 ETORICOXIB

PURPOSE

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

BACKGROUND

Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2).

The ADEC August 2002 meeting recommended the approval of XXXXXXXXX containing 60mg, 90mg and 120mg of etoricoxib for the treatment of symptoms and signs of osteoarthritis (OA), treatment of acute gouty arthritis, treatment of primary dysmenorrhoea and relief of acute pain related to minor dental procedures.

DISCUSSION

The Committee noted that etoricoxib was classified as 'prescription medicine' in New Zealand.

DECISION 2003/37 - 31

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

Schedule 4 - New entry

ETORICOXIB.

15.1.3 VALDECOXIB

PURPOSE

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

BACKGROUND

Valdecoxib is a non-steroidal anti-inflammatory drug (NSAID) reported to be a selective inhibitor of cyclooxygenase-2 (COX-2). Valdecoxib is the active form of the parenteral agent parecoxib and is structurally related to celecoxib and rofecoxib. These medicines were included in Schedule 4 when considered.

The ADEC August 2002 meeting recommended the approval of XXXXXXXXX containing 10mg, 20mg and 40mg of valdecoxib. The recommended indication was for

the symptomatic treatment of osteoarthritis and rheumatoid arthritis, treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures, and treatment of mild to moderate post-operative pain.

DISCUSSION

The Committee noted that valdecoxib was classified as 'prescription medicine' in New Zealand.

DECISION 2003/37 - 32

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

Schedule 4 - New entry

VALDECOXIB.

15.1.4 PEGFILGRASTIM

PURPOSE

The Committee considered the scheduling of pegfilgrastim, a medicine.

BACKGROUND

Pegfilgrastim is a covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (filgrastim, S4) and monomethoxypolyethylene glycol providing neutrophil support in patients with non-myeloid malignancies receiving chemotherapy.

The ADEC August 2002 meeting recommended the approval of XXXXXXXXX containing pegfilgrastim (rbe) 6 mg/0.6 mL in a ready-to-use syringe. The recommended indication was for the treatment of patients with cancer following chemotherapy to decrease the duration of severe neutropenia and so reduce the incidence of infection as manifested by febrile neutropenia.

DISCUSSION

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

DECISION 2003/37 - 33

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

Schedule 4 - New entry

PEGFILGRASTIM.

15.1.5 TELITHROMYCIN

PURPOSE

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

BACKGROUND

Telithromycin (HMR 3647) is a broad-spectrum antibiotic and the first in a new family called 'ketolides' which exhibits greater antibacterial activity than macrolides. The ketolides belong to a new class of semi-synthetic 14-membered ring antibacterial compounds within the macrolide family.

The ADEC October 2002 meeting recommended the approval of XXXXXXXXX containing telithromycin 400mg. The recommended indication was for the treatment in patients 18 years and older of community acquired pneumonia and for the treatment of acute exacerbations of chronic bronchitis, where there is demonstrated resistance to penicillins and/or macrolides in the pathogen-causing infection, or treatment failure after use of a first-line agent.

DISCUSSION

A member advised that the TGA, in line with the Commonwealth Government's response to the JETACAR Report, required a risk assessment of the potential for resistance development to be included in registration applications for products containing a new antibiotic substance. The member also stated that this requirement was also being applied to new products containing already approved antibiotics where the use pattern was modified. The Committee was informed that such risk assessments were routinely referred to the Expert Advisory Group on Antimicrobial Resistance (EAGAR) for their expert opinion.

(Paragraph deleted)

The Committee was advised that telithromycin was classified as 'prescription medicine' in New Zealand.

DECISION 2003/37 - 34

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

Schedule 4 - New entry

TELITHROMYCIN.

15.1.6 BOSENTAN

PURPOSE

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

BACKGROUND

Bosentan is a cardiovascular agent that belongs to a new group of compounds known as endothelin-receptor antagonists and has a two-fold higher affinity for ETA receptors than ETB receptors. By blocking both receptors, bosentan reduces the effect of endothelin 1 and improves pulmonary haemodynamics in animal models of pulmonary hypertension, decreasing pulmonary pressure and reducing the proliferation of pulmonary vascular smooth muscle.

The ADEC October 2002 meeting recommended the approval of XXXXXXXXX containing bosentan (as the monohydrate) 62.5 mg and 125 mg for the treatment of primary pulmonary hypertension or pulmonary hypertension associated with scleroderma in adults with WHO Class III or IV symptoms.

DISCUSSION

Members noted the ADEC October 2002 Meeting raised teratogenicity as a significant issue. The ADEC minutes stated that although there were no documented instances of teratogenicity of bosentan in humans, animal toxicity studies showed that the risk of birth defects occurring in the first 4-5 weeks of pregnancy was likely at exposures to effective dose levels. Consequently, the ADEC recommended that the registration of bosentan must be conditional upon the inclusion of a boxed warning statement advising that bosentan is contraindicated in pregnancy and that contraception must be used when taking this drug.

A member stated that bosentan would likely be prescribed by a medical specialist given the complexity of the medical condition to be treated, and the drug's potential contraindications and side effects, which included hepatoxicity and anaemia, required ongoing monitoring. Members also noted that hormonal contraceptives may fail if administered with bosentan due to drug-to-drug interaction, and agreed it was essential

for clear guidance to be given to patients regarding the use of appropriate contraceptive methods. On these grounds, the Committee, whilst supporting inclusion of bosentan in Schedule 4, considered the need for further controls under Appendix D and listing in Appendix F to allow labelling with appropriate pregnancy warning statements.

The Committee supported the inclusion of bosentan in Appendix D to limit the prescribing of bosentan to medical specialists only, given its high potential to cause birth defects and the likelihood that bosentan would be prescribed to women of child-bearing age. In addition, the Committee was of the view that requiring pregnancy warning statements on the label would optimise communication of potential hazards associated with the use of bosentan during pregnancy to patients.

The Committee also noted that the approved Product Information (PI) for XXXXXXXXX warned that "women must not become pregnant for at least three months after stopping treatment with XXXXXXXXX ".

The Committee was advised that bosentan was not a classified medicine in New Zealand.

DECISION 2003/37 - 35

The Committee agreed to include bosentan in Schedule 4 and Appendix D of the SUSDP, on the grounds that the condition being treated necessitated appropriate diagnosis and the use of this medicine required patient management and monitoring by a medical specialist. In addition, the Committee also agreed that the inclusion of pregnancy warning statements in Appendix F of the SUSDP was necessary to alert women to the high potential for birth defects to occur from exposure to bosentan during pregnancy.

Schedule 4 - New entry

BOSENTAN.

Appendix D, Part 6 - New entry

6. Poisons available only from or on the prescription or order of a specialist physician and for which the prescriber must, where the patient is a woman of child-bearing age:

(a) ensure that the possibility of pregnancy has been excluded prior to commencement of treatment; and

(b) advise the patient to avoid becoming pregnant during and for a period of 3 months after completion of treatment.

BOSENTAN for human use.

Appendix F, Part 3 - New entry

Bosentan

Warning Statements..... 7, 62, 76

15.1.7 DUTASTERIDE

PURPOSE

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

BACKGROUND

Dutasteride is an inhibitor of type 1 and 2 testosterone-5α-reductase and acts in a similar way to finasteride, which is indicated for the treatment and control of symptomatic benign prostatic hyperplasia (BPH), and the only other approved therapeutic agent in this class in Australia.

The ADEC October 2002 meeting recommended the approval of XXXXXXXXX containing 500µg of dutasteride for the treatment of patients with symptomatic benign prostatic hypertrophy (BPH) with an enlarged prostate.

DISCUSSION

The Committee noted that dutasteride is contraindicated for use in women based on preclinical data suggesting that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male foetus carried by a woman exposed to dutasteride.

The Committee considered the proposal to include pregnancy warning statements in Appendix F of the SUSDP, given that the Product Information (PI) for dutasteride also carried a precaution that the drug is absorbed through the skin, and that women and children must avoid contact with leaking capsules. However, members noted that the drug was not indicated for use in women and the risk of accidental exposure to the product by women and children was insignificant, based on the experience with finasteride. In addition, it was also noted that the product presentation, i.e. capsules in blister packs, should help to minimise the potential for accidental exposure to the drug.

The Committee noted that dutasteride was classified as 'prescription medicine' in New Zealand.

DECISION 2003/37 - 36

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

Schedule 4 - New entry

DUTASTERIDE.

15.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

There were no items considered.

16. OTHER MATTERS FOR CONSIDERATION

16.1 DEXTROMETHORPHAN

PURPOSE

The Committee reconsidered Trans-Tasman Harmonisation Working Party (TTHWP) Recommendation 13/6 to include a pack size limit of 600 mg dextromethorphan in Schedule 2 (S2) of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

BACKGROUND

The July 2000 TTHWP Meeting recommended that New Zealand (NZ) and Australia adopt TTHWP Recommendation 13/6, following the rescheduling of single-active preparations from S4 to S2 in February 1998. This amendment allowed in S2, both compounded and single-active preparations containing 30 mg or less of dextromethorphan for divided preparations and 0.3% or less of dextromethorphan for undivided preparations, when labelled with a recommended dose not exceeding 30 mg of dextromethorphan. Recommendation 13/6 was based on the view that imposing a pack size restriction of 600 mg in S2 was necessary to minimise the abuse and misuse potential associated with dextromethorphan products, particularly with the OTC availability of single-active preparations.

The February 2001 NDPSC Meeting endorsed TTHWP Recommendation 13/6 and recommended that NZ-MCC consider adopting this recommendation to harmonise with Australia. However, the NDPSC omitted to take further action to adopt TTHWP Recommendation 13/6 into the SUSDP and the Schedule 2 entry for dextromethorphan remained unchanged.

The May 2002 MCC Meeting considered TTHWP Recommendation 13/6 but did not agree to adopt this recommendation on the basis that abuse of dextromethorphan was not an issue in NZ, even for General Sale preparations. The October 2002 NDPSC Meeting noted the May 2002 MCC Minutes and agreed to reconsider TTHWP Recommendation 13/6 at the February 2003 meeting.

DISCUSSION

The Committee noted the pre-meeting comments from XXXXXXXXX opposing any further restrictions on dextromethorphan such as those, which aimed to restrict the pack size in Schedule 2 in the absence of evidence of abuse in Australia. On these grounds, XXXXXXXXX supported harmonisation of the scheduling of dextromethorphan with NZ.

The Committee was advised that there was no evidence of abuse of 'general sale' dextromethorphan products in New Zealand such as lozenges containing 15 mg dextromethorphan and undivided preparations containing 0.25% dextromethorphan. This member also stated that if there was no evidence of dextromethorphan abuse in Australia then this could be the basis for harmonising the scheduling of dextromethorphan in the two countries.

A member stated that forensic evidence was available to show that dextromethorphan products including lozenges continued to be a target for abuse and diversion to the illicit drug trade in some jurisdictions, although diversion of dextromethorphan was not as widespread as that of pseudoephedrine. Members noted the extensive promotion of abuse of dextromethorphan on the Internet, which included credible and highly detailed information on how to extract the drug from various types of cough medicines.

The Committee did not support harmonisation with NZ on the view that it was inappropriate to make products with a long history of being abused or misused available without any controls on availability.

The Committee was advised that a review of products listed on the ARTG suggested that all products, i.e. divided and undivided, currently listed on the ARTG contained less than 600 mg of total dextromethorphan per pack. On this basis, there was no expected regulatory impact on existing products should a pack size limit of 600 mg dextromethorphan be adopted.

DECISION 2003/37 - 37

The Committee agreed not to harmonise with New Zealand at this time and adopted TTHWP Recommendation 13/6 to include a pack size restriction of 600 mg dextromethorphan for all preparations in Schedule 2 (S2). The Committee remained concerned over the potential for products containing dextromethorphan in S2 to be abused or diverted into the illicit drug trade and restricting the pack size should assist in reducing this potential.

Schedule 2 – Amendment (see item 14.1.3)

16.2 3-AMINOBENZOIC ACID ETHYL ESTER METHANESULPHONATE

PURPOSE

The Committee considered the recommendations of New Zealand MCC on the scheduling harmonisation of 3-aminobenzoic acid ethyl ester methanesulphonate.

BACKGROUND

3-Aminobenzoic acid ethyl ester methanesulphonate was a fish anaesthetic.

Recommendation 48/6 of the July 2000 TTHWP proposed that the New Zealand MOH include in Part I (equiv. to Schedule 4) of the Schedule the following substances:

3-AMINOBENZOIC ACID ETHYL ESTER METHANESULPHONATE
AMYLOCAINE
BUTACAINE
DIPERODON
ETIDOCAINE
ORTHOCAINE

The February 2001 NDPSC meeting endorsed TTHWP's recommendation on harmonisation grounds and noted that these substances were already listed in Schedule 4 of the SUSDP.

The May 2002 New Zealand MCC meeting considered Recommendation 48/6 and agreed to include amylocaine, butacaine, diperodon, and etidocaine in Part 1. However, New Zealand MCC did not agree to include 3-aminobenzoic acid ethyl ester methanesulphonate in their Schedule on the basis that this substance was no longer listed in Martindale, suggesting it was an obsolete compound. Additionally, no products are registered in New Zealand containing 3-aminobenzoic acid ethyl ester methanesulphonate. Accordingly, New Zealand MCC proposed that the NDPSC consider deleting 3-aminobenzoic acid ethyl ester methanesulphonate from Schedule 4 of the SUSDP, if no products containing these substances were listed/registered on the ARTG.

The October 2002 NDPSC Meeting agreed to gazette the proposed deletion of 3-aminobenzoic acid ethyl ester methanesulphonate for consideration at the February 2003 NDPSC meeting.

DISCUSSION

The Committee noted that there were no registered products on the ARTG or on PUBCRIS containing 3-aminobenzoic acid ethyl ester methanesulphonate for human or

veterinary use. A search of the internet did not produce any products containing 3-aminobenzoic acid ethyl ester methanesulphonate.

DECISION 2003/37 - 38

The Committee agreed to delete 3-aminobenzoic acid ethyl ester methanesulphonate from Schedule 4 of the SUSDP on harmonisation grounds.

Schedule 4 - Amendment

3-AMINOBENZOIC ACID ETHYL ESTER METHANESULPHONATE - delete entry

16.3 ORTHOCAINE

PURPOSE

The Committee considered the recommendations of New Zealand MCC on the scheduling harmonisation of orthocaine.

BACKGROUND

Recommendation 48/6 of the July 2000 TTHWP proposed that the New Zealand MOH include in Part I (equiv. to Schedule 4) of the Schedules the following substances:

3-AMINOBENZOIC ACID ETHYL ESTER METHANESULPHONATE
AMYLOCAINE
BUTACAINE
DIPERODON
ETIDOCAINE
ORTHOCAINE

The February 2001 NDPSC meeting endorsed TTHWP's recommendation on harmonisation grounds and noted that these substances were already listed in Schedule 4 of the SUSDP.

The May 2002 New Zealand MCC meeting considered Recommendation 48/6 and agreed to include amylocaine, butacaine, diperodon, and etidocaine in Part 1. However, New Zealand MCC did not agree to include orthocaine in their Schedules on the basis that this substance was no longer listed in Martindale, suggesting it was an obsolete compound. Additionally no products are registered in New Zealand containing orthocaine. Accordingly, New Zealand MCC proposed that the NDPSC consider deleting orthocaine from Schedule 4 of the SUSDP, if no products containing these substances were listed/registered on the ARTG.

The October 2002 NDPSC Meeting agreed to gazette the proposed deletion of orthocaine for consideration at the February 2003 NDPSC meeting.

DISCUSSION

The Committee noted that there were no registered products on the ARTG or on PUBCRIS containing orthocaine for human or veterinary use. A search of the internet did not produce any products containing orthocaine.

DECISION 2003/37 - 39

The Committee agreed to delete orthocaine from Schedule 4 of the SUSDP on harmonisation grounds.

Schedule 4 - Amendment

ORTHOCAINE - delete entry

16.4 BENZAMINE

PURPOSE

The Committee considered the recommendation of New Zealand MCC on the scheduling harmonisation of benzamine.

BACKGROUND

Recommendation 51/6 of the July 2000 TTHWP proposed that the NDPSC delete the Schedule 2 entry and retain the Schedule 4 entry for benzamine in the SUSDP. TTHWP also recommended that the New Zealand MOH include benzamine in Part I (equiv. to S4) of their Schedule, subject to there being no general sales products containing the substance.

The February 2001 NDPSC meeting endorsed TTHWP's recommendation on harmonisation grounds and deleted the Schedule 2 entry for benzamine in the SUSDP.

The May 2002 New Zealand MCC meeting rejected the TTHWP recommendation as benzamine was not scheduled in New Zealand, had no reference in Martindale and was not contained in any registered products in New Zealand. Accordingly, the New Zealand MCC proposed that the NDPSC consider deleting benzamine from Schedule 4 of the SUSDP if no products containing benzamine were listed/registered on the ARTG.

The October 2002 NDPSC meeting agreed to gazette the proposed deletion of benzamine for consideration at the February 2003 NDPSC meeting.

DISCUSSION

The Committee noted that there were no registered products on the ARTG or on PUBCRIS containing benzamine for human or veterinary use.

DECISION 2003/37 - 40

The Committee agreed to delete benzamine from Schedule 4 of the SUSDP on harmonisation grounds.

Schedule 4 - Amendment

BENZAMINE - delete entry

16.5 IBUPROFEN

PURPOSE

The Committee considered the recommendation of New Zealand MCC on the scheduling harmonisation of ibuprofen.

BACKGROUND

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

The November 2000 TTHWP Meeting made - Recommendation No. 33/7 - that NZ MOH adopt the revised wording of the SUSDP (15) (2) 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 Recommendation No. 33/7.

The May 2002 MCC meeting considered TTHWP Recommendation No. 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 4 grams 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.

- The NDPSC adopt the MCC recommendation limiting the concentrations of liquid ibuprofen permitted in pharmacy-only (S2) medicines.

The October 2002 Meeting agreed to gazette the consideration of scheduling of ibuprofen for consideration at the February 2003 meeting.

DISCUSSION

The Committee noted that there was harmonisation on pack size. New Zealand, however, had adopted dose limitations into their Regulatory Guidelines and New Zealand MCC were recommending harmonisation on strengths.

The Committee noted the pre-meeting comment from XXXXXXXXX objecting to the inclusion of a dose limit for the Schedule 2 entry for ibuprofen. This was made on the basis that New Zealand had included the dose limit for ibuprofen in the NZ Regulatory Guidelines and not in the First Schedule to the Medicines Regulations. XXXXXXXXX felt that it was more appropriate to include this level of detail in the Australian Guidelines for the Registration of Medicines (AGRD vol 2), not through scheduling. This approach was considered consistent with the current paracetamol guideline in the AGRD that specifies concentrations that may be supplied. XXXXXXXXX suggested that the NDPSC recommend to the Medicines Evaluation Committee (MEC) to include these concentration limits for ibuprofen in the AGRD (volume 2).

The Committee was advised that the draft report of the TGA Review of Non-Prescription Analgesics had been released and that MEC would decide on the final recommendations which may include some items for NDPSC consideration.

OUTCOME

The Committee agreed that the Schedule 2 entry for ibuprofen remained appropriate and that the scheduling of ibuprofen would remain unharmonised at this time.

16.6 SELENIUM

PURPOSE

The Committee considered the New Zealand MCC proposal to harmonise with NZ by rescheduling selenium to Schedule 2 for external medicines containing more than 2.5%.

BACKGROUND

Selenium sulfide has antifungal and antiseborrhoeic properties and has been used as a 2.5% and a 1% shampoo for the treatment of dandruff (*pityriasis capitis*) and seborrhoeic dermatitis of the scalp. It is also used as a 2.5% lotion in the treatment of pityriasis versicolor. Selenium is an essential trace element and is an integral part of the enzyme system glutathione peroxidase protecting intracellular structures against oxidative damage. Overdosage of selenium has been associated with loss of hair, nail changes, diarrhoea, dermatitis, garlic odour of breath, fatigue, and peripheral neuropathy.

The February 2001 NDPSC meeting considered TTHWP's Recommendation 36/7 advising the NDPSC to recommend to NZ MCC to shift preparations for external use containing 2.5% selenium from Part III to Part I. This recommendation was made on the basis that prolonged use on broken skin has resulted in systemic toxicity. The NDPSC endorsed recommendation 36/7 and referred the matter to NZ for consideration.

The November 2002 NZ MCC meeting considered the TTHWP 36/7 but NZ MCC did not support it on the basis that it would make the scheduling of external products more restrictive compared to internal products, as internal products containing more than 150 micrograms per recommended daily dose would remain pharmacy only. Selenium products are currently general sale or pharmacy-only in New Zealand, there is no prescription category for selenium. MCC has recommended that the classification of selenium for external use remain unchanged and that NDPSC consider harmonisation with the NZ classification.

The toxicity of selenium sulfide shampoos when ingested by children was discussed at the April 1994 meeting of the NDPSC. It was concluded that the hazard associated with ingestion of the 1% solution was comparable to the 2.5% solution. The volume of the 2.5% selenium solution needed to cause death in a 20kg child is approx. 98mL, however selenium sulfide is an emetic and most of the solution would likely be expelled through vomiting. The volume remaining in the child's stomach after vomiting was estimated to be 12.5mg/kg which is below the single oral LD50 for the rat which is 78-120mg/kg.

DISCUSSION

The Committee noted that selenium sulfide has a different toxicity profile to selenium, although it can be highly toxic when ingested. Only traces of selenium sulfide are absorbed through intact skin, but prolonged use on broken skin has resulted in systemic toxicity.

The Committee understood that there have been 5 cases of non-life threatening adverse reactions recorded since 1983 including contact dermatitis, headache, rash and skin discolouration. A library internet search produced no evidence of poisoning through the use of selenium shampoos. A Member noted that there were no topical products for human use containing more than 2.5% selenium registered in either Australia or New Zealand.

The Committee noted that it appeared that the rationale for MCC's argument in not adopting Recommendation 36/7 was on the basis that harmonising with Australia creates a prescription only classification for selenium for external use in New Zealand when there is no existing prescription classification for selenium for internal use.

A Member noted that selenium shampoos used to be packaged in bottles with screw top lids that enabled a child to ingest a large volume of shampoo in a short period of time. These shampoos are now packaged in bottles with lids that expel the liquid at a much slower rate, thereby reducing the volume that may be ingested by a child.

The Committee noted that the origin of the schedule entry for topical selenium products was unknown. The Committee felt that further consideration of scheduling of topical selenium products could continue when the history and reasons for this schedule entry were known.

OUTCOME

The Committee agreed to defer the consideration of the scheduling of selenium for topical use to the June 2003 Meeting to enable further information to be presented.

16.7 SILVER SULFADIAZINE

PURPOSE

The Committee considered the New Zealand MCC proposal to include silver sulfadiazine in packs containing 50g or less of silver sulfadiazine Schedule 2 of the SUSDP.

BACKGROUND

Silver sulfadiazine is a sulfonamide/silver complex used in conjunction with debridement, as a 1% cream for the prevention and treatment of infection in severe burns. It has also been used in other skin conditions, such as leg ulcers, where infection may prevent healing and for the prophylaxis of infection in skin grafting. It has also been applied to the eyes in the treatment of superficial Aspergillus infections.

Silver sulfadiazine has broad antimicrobial activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, and some yeasts and fungi. Silver sulfadiazine has a bactericidal action; in contrast to sulfadiazine, the silver salt acts primarily on the cell membrane and cell wall and its action is not antagonised by p-aminobenzoic acid. Resistance to silver sulfadiazine has been reported and may develop during therapy.

The November 2001 NDPSC meeting considered the scheduling of silver sulfadiazine (SSDZ) in relation to the implementation for the JETACAR Recommendation 6. The Committee noted that resistance still remained a potential problem for SSDZ and in the absence of data to support relaxation of the scheduling of SSDZ, the Committee agreed

that it remained appropriately scheduled in Schedule 4. NDPSC recommended that New Zealand consider adopting a similar scheduling outcome.

The May 2002 MCC meeting considered the recommendation from the November 2001 NDPSC meeting in relation to SSDZ and agreed that pack sizes of 50g or less remained appropriately scheduled as a pharmacy-only medicine in New Zealand (above 50g is prescription). Accordingly, MCC recommended that NDPSC consider adopting a similar classification for SSDZ to allow harmonisation. The October 2002 Meeting agreed to gazette the consideration of scheduling of silver sulfadiazine for discussion at the February 2003 meeting.

DISCUSSION

The Committee noted the basis of the MCC's decision to retain a pharmacy-only classification for silver sulfadiazine when in pack sizes 50g or less. The MCC referred to the NDPSC report on ophthalmic sulfacetamide which stated that there were no significant antibiotic resistance issues for sulfonamides, including SSDZ. The MCC stated that restricting access would not increase resistance, but could worsen resistance problems by causing other antibiotics to be used and that OTC use of SSDZ was appropriate for the treatment of minor burns.

The Committee noted that advice was sought from the Medicines Evaluation Committee (MEC) on the appropriateness of rescheduling pack sizes 50g or less of SSDZ, given the currently registered indications for SSDZ products. MEC members in general did not support the MCC proposal on the basis that there has been some reports of delayed wound healing following the use of SSDZ on burns and the potential for resistance to develop. A MEC member also highlighted the need for a warning statement against prolonged use of SSDZ and the need for a medical review if the lesion/burn remained unresolved.

The Committee noted that comment had also been received from a TGA evaluator within the OTC Medicines Section. The evaluator highlighted that if the indication for OTC use included treatment of infections of burns, it is likely that this would create a hazard for consumers treating a potentially deep-seated infection with a topical preparation. It is stated that leg ulcers and pressure sores require medical attention under most circumstances, especially in long term diabetics with vasculopathies and neurophathies, who may not feel or sense any swelling or pain associated with a leg infection. The evaluator also noted that experience with silver sulfadiazine in community pharmacies is limited and this lack of knowledge needs to be addressed before rescheduling is considered. The evaluator indicated that it would be best to retain SSDZ in S4.

The Committee noted that advice on the MCC proposal had also been sought from EAGAR. EAGAR indicated that it does not support the MCC proposal on the grounds that silver sulfadiazine can select for resistance to sulfonamides and silver ions, and that sulfonamides are still widely used in human medicine for the systemic treatment of infections and considered valuable therapeutic agents. The S2 availability of silver

sulfadiazine would be likely to result in increased exposure and therefore increased selective pressure for resistance.

OUTCOME

The NDPSC agreed that the Schedule 4 entry for silver sulfadiazine remains appropriate on the basis of the advice received from MEC and EAGAR and that the scheduling of silver sulfadiazine will remain unharmonised with NZ at this time.

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

No items were considered.

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

18.1 SODIUM PICOSULFATE

PURPOSE

The Committee considered the New Zealand MCC recommendation to include sodium picosulfate for oral laxative use in Schedule 4.

BACKGROUND

The October 2002 NDPSC meeting considered the foreshadowed inclusion of sodium picosulfate (and macrogol 3350) in preparations for oral laxative use in Schedule 4 of the SUSDP. NDPSC agreed that the unscheduled status of sodium picosulfate and macrogol 3350 for laxative use remained appropriate on the grounds that there were no reports of adverse events or misuse associated with laxative use of these substances.

The November 2002 NZ MCC meeting considered a proposal from XXXXXXXXX, sponsor of XXXXXXXXX in New Zealand, to reschedule sodium picosulfate when used as a laxative to prescription medicine (S4) and to restricted medicine (S3) when used for bowel cleansing prior to diagnostic, medical or surgical procedures.

DISCUSSION

The NZ member advised the Committee that the classification of sodium picosulfate, as agreed to by the November 2002 NZ MCC meeting, had been gazetted as XXXXXXXXX did not provide NZ MCC with any significant data arguing against the classification decision. NZ MCC, however, is expecting to receive an application for reconsideration of the decision.

The Committee noted the overlap of advice between the NDPSC and NZ MCC, in that the outcome of the October 2002 NDPSC meeting had not been available for consideration at the November 2002 NZ MCC meeting.

OUTCOME

NZ MCC to reconsider classification of sodium picosulfate for laxative use.

18.2 SOLANACEOUS PLANTS AND ALKALOIDS

PURPOSE

The Committee considered the New Zealand MCC recommendation to increase the cut-off for exemption of dilute preparations in Appendix G of the SUSDP for atropine, hyoscine and hyoscyamine to harmonise with New Zealand.

BACKGROUND

The November 2002 NZ MCC meeting considered a submission from XXXXXXXXX proposing to change the level for exemption for scheduling for solanaceous alkaloids on the grounds that the existing cut-offs in Appendix G of the SUSDP were too low for the plant alkaloids. XXXXXXXXX proposal has been based on the principle where herbal medicines containing one hundredth of the minimum lethal dose of solanaceous alkaloids per pack can be sold as 'general sale'. NZ MCC considers this approach still appropriate on a safety perspective and has agreed that raising the cut-off for exemption to 300 mcg per litre or per kilo for atropine, hyoscine and hyoscyamine in 'general sale' homeopathic preparations still provides a 100-fold safety factor.

The November 2002 NZ MCC meeting also noted that the existing inconsistency in the New Zealand classifications, where the cut-offs for exemption applying to both the plant material and its alkaloids, were being amended to express these cut-offs in terms of the total alkaloid content.

DISCUSSION

The meeting was advised that XXXXXXXXX had put forward cut-off points which were either too high or too low, depending on which way they were applied. The 10mg/kg of alkaloid was too high but 10mg/kg of the herb was too low. The submission included a request to try and solve the problem by using a process which had been agreed to previously to treat a sensible cut-off point for alkaloids that was consistent across all solanaceous alkaloids. The New Zealand submission was based on a framework which related to fractions of the lethal dose cut-off. Although the framework had not been agreed to as a general principle for the scheduling of all products, the NZ MCC felt it was reasonable to apply it in this case to gain consistency across all the solanaceous alkaloids. Using the framework, where a minimum lethal dose is known the cut-off to pharmacy-

only should be set at $^{1}/_{10}$ of the lethal dose and the cut-off to general sale should be set at $^{1}/_{100}$ of the lethal dose.

A Member recalled that the Appendix G exemptions were included in the SUSDP to ensure that homeopathic preparations were not scheduled. Another Member stated that these substances had higher cut-offs compared with other homeopathic ingredients.

The Committee agreed that this was not a scheduling issue, but a deregulation or exemption issue under Trans-Tasman where the cut-off for scheduling of alkaloids is applied through Appendix G. The Members agreed this issue required further consideration by the Committee.

The Committee agreed to foreshadow this item for further consideration at the June 2003 meeting and noted that the Record of Reasons would provide industry with details to enable them to respond appropriately to the gazette notice.

OUTCOME

The Committee agreed to defer consideration of solanaceous alkaloids to the June 2003 meeting to allow gazettal of the consideration.

18.3 GLYCERYL TRINITRATE & ISOSORBIDE DINITRATE

PURPOSE

The Committee noted the harmonisation of the Australian and New Zealand scheduling of glyceryl trinitrate and isosorbide dinitrate.

BACKGROUND

The November 2000 NDPSC meeting agreed to reschedule oral preparations containing glyceryl trinitrate and oral preparations containing 10mg or less of isosorbide dinitrate per dose unit from Schedule 2 to Schedule 3.

The November 2002 NZ MCC supported the view that these substances would be more appropriately classified as restricted medicines for their existing indications and agreed to harmonise with Australia.

DISCUSSION

The Committee noted that New Zealand MCC had agreed to adopt glyceryl trinitrate and isosorbide dinitrate as restricted medicines in the interest of harmonisation.

OUTCOME

The Australian and New Zealand scheduling of glyceryl trinitrate isosorbide dinitrate is harmonised.

18.4 NICOTINE FOR INHALATION

PURPOSE

The Committee noted harmonisation of nicotine for inhalation.

BACKGROUND

The February 2002 NDPSC meeting agreed to the rescheduling of nicotine inhalation for use as an aid in withdrawal from tobacco smoking, from S3 to S2. The decision was made on the basis that nicotine for inhalation has good safety and side-effect profile, which is consistent with other NRT products including the chewing gum. NDPSC recommended that NZ MCC consider adopting a similar scheduling outcome.

The November 2002 NZ MCC meeting agreed to harmonise with Australia and recommended that nicotine for inhalation be reclassified from restricted medicine (S3) to pharmacy-only medicine (S2) except when sold from a smoking cessation clinic run under the auspices of a registered medical practitioner, nurse, pharmacist or psychologist. MCC agreed that the current exemption from classification status when used in smoking cessation clinics run by appropriate registered health professionals should continue to apply.

DISCUSSION

The Committee noted that NZ MCC agreed to include nicotine for inhalation in Part II as pharmacy-only medicine except when supplied through a smoking cessation clinic run by appropriate healthcare professionals.

OUTCOME

The outcome of the scheduling of nicotine inhalers in Australia and New Zealand is harmonised.

18.5 CLOBETASONE

PURPOSE

The Committee considered the NZ MCC decision on clobetasone.

BACKGROUND

The February 2002 NDPSC meeting agreed to the scheduling of clobetasone in Schedule 3, when in preparations for dermal use containing 0.05% or less of clobetasone in packs

containing 30 g or less, for use in adults and children 12 years and over. The decision was based on the safety profile of 0.05% clobetasone for dermal use, which is comparable to 1% hydrocortisone cream, and the product having a long history of safe use worldwide. In addition, the conditions being treated can be appropriately managed by consumers with pharmacist advice, and the product has a well-characterised side effect profile. Appropriate Appendix F warning statements were also recommended. NDPSC recommended that NZ MCC consider adopting a similar scheduling outcome

The November 2002 NZ MCC did not agree to harmonisation and recommended that 0.05% topical clobetasone should remain a prescription medicine pending further information. NZ MCC felt that more information was required about the use and safety of mild to moderate potent corticosteroids before a recommendation could be made about reclassification

DISCUSSION

The Committee noted that NZ MCC did not agree to harmonisation, pending consideration of further information on the use and safety of mild to moderately potent corticosteroids. The Committee agreed that Australian and New Zealand scheduling of clobetasone remain unharmonised.

OUTCOME

Australia and New Zealand remain unharmonised over the scheduling of dermal preparations containing 0.05% or less of clobetasone.

19. INITIAL REVIEW/FORMAL OPINIONS (PHARMACEUTICALS)

There were no items considered.