



**Australian Government**  
**Department of Health and Ageing**  
**Therapeutic Goods Administration**

# National Drugs and Poisons Schedule Committee

Record of Reasons

42nd Meeting  
12-14 October 2004

Section 52D(2) of the *Therapeutic Goods Act 1989* (the Act) provides the power for the NDPSC to amend the Poisons Standard or prepare a new Standard. The NDPSC takes into account relevant matters mentioned in Section 52E of the Act when making a scheduling decision.

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

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## **GLOSSARY**

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

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

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

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



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**1.7.1 OPERATIONS/POLICIES OF THE COMMITTEE**

[Items Removed]

**1.7.1.4 APPENDIX E**

**PURPOSE**

The Committee was informed that the old standard statements in Appendix E had expired on 31 August 2004.

**BACKGROUND**

At the November 2000 NDPSC meeting, the Committee made a number of amendments to the Appendix E Introduction and the new statements to be contained in Appendix E Part 1.

At the February 2001 NDPSC meeting, the Committee agreed that the two year transition period (1 September 2001 – 31 August 2003) apply to those labels that currently include any of the OLD statements b, h, r, or v, or will include the NEW standard statement G3. All other labels to have a three-year transition period (1 September 2001 – 31 August 2004) to change over to the new statements. The relevant statements in the proposed Appendix E, Introduction were amended to reflect this change.

Manufacturers, packers and suppliers were encouraged to replace existing first aid instructions with New Standard Statements as soon as practical, but no later than 31 August 2003 for those substances requiring statement G3 and no later than 31 August 2004 for all other statements.

**OUTCOME**

Members noted that the transition period was now over and the NEW Standard Statements came into effect on 31 August 2004. It was agreed that the OLD statements be removed from Appendix E at the time of publication of SUSDP 20.

[Items Removed]

**1.8 NDPSC WORKING PARTIES**

**1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY**

[Item Removed]

### **1.8.1.2 ANTIBIOTIC SUBSTANCES (NISIN)**

#### **PURPOSE**

The Committee considered advice from the TTHWP that the antibiotic nisin could now be removed from the 2-year list.

#### **BACKGROUND**

The Committee recalled that nisin is a polypeptide antibiotic produced by *Streptococcus laxctis* and is approved as a food additive in Australia. It is 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.

The 6<sup>th</sup> TTHWP meeting had been advised that in November 1998, the New Zealand Medicines Classification Committee (MCC) agreed to adopt the Schedule 4 generic statement for antibiotic substances that read:

Schedule 4:

ANTIBIOTIC SUBSTANCES **except:**

- (a) when separately specified in these schedules; or
- (b) nisin.

Since November 1998 MCC decision, nisin is no longer listed on the New Zealand Classification of Medicines database. In Australia, nisin is included in Appendix B on the basis of its low toxicity and food use. There are no products listed on the ARTG.

#### **DISCUSSION**

The NDPSC was advised that 11<sup>th</sup> TTHWP meeting had noted that the scheduling for nisin was now “essentially harmonised” and agreed that the NDPSC should be advised that the entry for nisin could be removed from the 2-year list.

#### **OUTCOME**

The Committee agreed to remove nisin from the 2-year list.

### **1.8.1.3 STRYCHNOS SPP**

#### **PURPOSE**

The Committee considered the harmonisation of the scheduling of *Strychnos spp*, particularly the cut-off for exemption from scheduling of dilute preparations containing *Strychnos spp*.

## BACKGROUND

The Committee noted that 11<sup>th</sup> TTHWP meeting had identified that the differences between scheduling of *Strychnos spp* in Australia and New Zealand centred around the cut-off for exemption for *Strychnos spp*. In Australia the cut-off for exemption was 10 mg/kg whereas in the New Zealand classification, the cut-off for exemption for *Strychnos spp*. was based on strychnine and set at 1 mg/kg or litre. Strychnine was not separately listed in the schedules in New Zealand.

To achieve the least restrictive approach to harmonisation, the TTHWP identified that New Zealand would need to consider amending the classification to exempt products containing 10 milligram or less per kilogram or litre of *Strychnos spp*. At the same time, the TTHWP noted that, from a compliance and enforcement perspective, it would be preferable to specify the cut-off in terms of the alkaloid content, ie strychnine.

The TTHWP had agreed to recommend to the NDPSC that the New Zealand Ministry of Health (MOH) consider harmonising with Australia by adopting the least restrictive approach to scheduling viz to adopt the Australian scheduling and set the cut-off level at 10 mg/kg or litre of *Strychnos spp*. However, prior to consideration of the matter at the October 2004 NDPSC meeting, the TTHWP requested further research in respect to the level of strychnine in *Strychnos spp* and any evidence of adverse health effects associated with the use of *Strychnos spp*.

## DISCUSSION

The NDPSC noted that since the June 2004 TTHWP meeting, advice had been received in respect to the strychnine content of *Strychnos spp*, and also information about the safety of *Strychnos spp* products. The Office of Complementary Medicines (OCM) had noted that, within Australia, only *Strychnos nux-vomica* and *Strychnos ignatii* were permitted for use in complementary medicines. OCM also advised the strychnine content of *Strychnos spp* (Table 1).

Table 1: Strychnine content in *Strychnos* species

SPECIES	SEED	STEM	LEAF	ROOT	Comments
<i>Strychnos angustiflora</i>	Less than 0.001%•	ND•	ND•	ND•	Seeds, bark and young leaves reported to contain strychnine. Used medicinally in China
<i>Strychnos cathayensis</i>		0.01%•	0.16%•	0.01%•	Roots and seeds medicinal, leaves and seeds poisonous in China
<i>Strychnos ignatii</i>	3.94%•	1.23%•	0.31%•	0.38%•	Ignatius beans. Used medicinally in China
<i>Strychnos lucida</i>	0.1-0.84% <sup>3</sup>	Bark: 1.1% <sup>3</sup>	0.4-0.8% <sup>3</sup>		Fruit also contains strychnine <sup>3</sup>
<i>Strychnos nitida</i>	0.02%•	0.003%•	0.01%•	0.003%•	Fruit medicinal in China, seeds poisonous
<i>Strychnos nux-blanda</i>	0.02%•		ND•		
<i>Strychnos nux-vomica</i>	0.88%• 1.23%*	0.03%•	ND•		Medicinal use in China and India
<i>Strychnos ovata</i>	0.01%•	0.03%•	0.01%•	0.01%•	

SPECIES	SEED	STEM	LEAF	ROOT	Comments
<i>Strychnos ovata</i> <i>var confertiflora</i>		0.03%•	0.87%•	0.16%•	
<i>Strychnos potatorum</i>	ND*				Used in India for clearing water
<i>Strychnos umbellata</i>	ND•	0.01•	ND•	ND•	Seeds and roots reported to contain strychnine
<i>Strychnos wallichiana</i>	5.63%•	0.02%•	0.02%•	0.003%•	Used medicinally in China

ND: Not detected

• Gu Zp, Zhang CL, Lian WY, Xiao PG, Chen JM Determination of strychnine and brucine in *Strychnos* by HPLC *Acta Pharmaceutica Sinica* 1997, 32 (10): 791-794

\* Tease and Evans (2002) Pharmacognosy WB Saunders Toronto

<sup>3</sup> Bisset NG and Philipson JD The Asian species of *Strychnos*. Part IV. The Alkaloids (1976)

*Lloydia* Vol

39, No 5 pg 263325

The OCM noted that strychnine is fatal to man at doses of 30-90 mg and reported two adverse drug reaction reports involving *Strychnos nux-vomica*. Neither of the two products involved with these adverse reactions was listed on the ARTG.

- ADR no 198685 (04/07/2004) involved a female who became paranoid, irritable and cold after ingesting a homoeopathic medicine (containing 7 ingredients, one of which was *nux vomica*) combined with alcohol.
- ADR no 175190 (26/04/2002) described a 67 yr old female who developed angioedema 15mins after ingesting a product called 'XXXXXXXXXX' (containing numerous ingredients, one of which was *S. nux vomica*).

Reports in the open literature in regard to strychnine poisoning confirmed the strychnine content of 'Maqianzi' (the dried ripe seed of *Strychnos nux-vomica*) as being in the range of 1.00 – 1.4 per cent. The seed of *Strychnos ignatii* was noted by OCM to contain up to 3.94 per cent strychnine. Fatal doses of strychnine have been reported overseas to be as low as 5-10 mg. The lethal dose was generally reported at approximately 30-100 mg.

While the TTHWP had recommended harmonisation based on 10 mg/kg *Strychnos spp*, ie the least restrictive approach, it was noted that it might be preferable that harmonisation take into account the preference from a compliance perspective, to harmonise on strychnine. This would also avoid uncertainties in compliance arising from different levels of strychnine in various plant parts and across species.

The Committee also noted advice from OCM in respect to the strychnine content of the mother tinctures (the mother tincture is the original herbal tincture which is subsequently diluted and succussed to make homoeopathic potencies), of *Strychnos nux vomica*. The French Pharmacopoeia dictated a minimum level of 0.12 per cent, and a maximum level of 0.13 per cent strychnine. The German Homoeopathic Pharmacopoeia dictated a minimum of 0.18 per cent and a maximum of 0.2 per cent of strychnine and brucine, of which not more than 55 per cent of the homeopathic mixture is strychnine, in the mother tincture.

OCM had also noted that under current Australian regulations for homeopathic medicines, any homeopathic preparation that is a 1000 fold dilution (or a lesser dilution) of the mother tincture is required to be Listed on the ARTG. This generally equated to potencies 3X or below. Any remedy more dilute than this was therefore likely to have a maximum of 0.000013 per cent strychnine, which was below the maximum permitted cut-off level. There was also a wide safety margin compared against reported low-level fatal doses and the accepted lethal dose.

The NDPSC noted that there were currently approximately 62 products listed as containing *Strychnos nux-vomica* or *Strychnos ignatii*, included in the ARTG and two export listed products. All of these products were homoeopathic.

## OUTCOME

The Committee agreed to foreshadow the harmonisation of the scheduling of *Strychnos spp* with New Zealand by deleting the Appendix G entry for *Strychnos spp* and amending the Schedule 4 entry in line with the New Zealand classification.

## FORESHADOWED DECISION (for consideration at the February 2005 meeting)

### Schedule 4 - Amendment

STRYCHNOS spp – amend entry to read:

STRYCHNOS spp **except** in preparations containing 1 milligram or less per litre or per kilogram of strychnine.

### Appendix G - Amendment

STRYCHNOS spp – delete entry

[Item removed]

## 1.8.1.5 SALBUTAMOL AND TERBUTALINE

### PURPOSE

The Committee considered the harmonisation of the scheduling for salbutamol and terbutaline.

### BACKGROUND

At its 11<sup>th</sup> meeting in July 2004, the Trans- Tasman Harmonisation Working Party (TTHWP) noted that the scheduling of salbutamol and terbutaline had been reviewed by the NDPSC in 2000/2001 as part of the Trans-Tasman medicines scheduling harmonisation project between Australia and New Zealand. This consideration was open

to public comment. The November 2000 NDPSC Meeting considered that "... there appeared to be no new significant safety issues associated with Schedule 3. There were some issues of concern but there was a lack of evidence to suggest that rescheduling (to Prescription Only) would result in better asthma management". The NDPSC confirmed "... its continuing support for inclusion of salbutamol and terbutaline in Schedule 3"

In contrast, terbutaline (tablets and elixir) and salbutamol (syrup and tablets) were listed in Part I in New Zealand.

The Working Party noted that the current position in respect to the scheduling of formulations containing salbutamol or terbutaline was as listed in the table below. Formulation types containing terbutaline or salbutamol which are yet to be harmonised are identified.

Type of Formulation	SUSDP Schedule	New Zealand Schedule
<b>TERBUTALINE</b>		
Injection, nebulising solution.	S4	Part I
▲ Terbutaline in aerosols delivering 250 micrograms or less per metered dose or in dry powders delivering 500 micrograms or less per dose.	S3	Part I
Terbutaline tablets and elixir	S4	Part I
<b>SALBUTAMOL</b>		
▲ Inhaler and autoinhaler in metered aerosols delivering 100 micrograms or less per metered dose or in dry powders for inhalation delivering 200 micrograms or less per dose	S3	Part I
Disks, respirator solution and nebules, injection	S4	Part I
Syrup, Tablets	S4	Part I

The Working Party recalled that the MCC 25th meeting in May 2001 noted that there was overwhelming objections raised during the consultation process to the proposal to make inhaled dose forms of salbutamol and terbutaline available as over-the-counter (OTC) medicines. The 25th meeting of MCC also considered other factors including the non-availability to specialist nurses should reclassification to a pharmacist only (Part II) classification go ahead. Retention of the prescription medicine classification was considered appropriate to retain the provision allowing the supply of these medicines through suitably accredited nurses. MCC was strongly opposed to further harmonisation with Australia and agreed to advise the NDPSC that "MCC had opted not to harmonise with Australia on the classification of inhaled salbutamol and terbutaline because of differing disease rates and means of access to treatment between the two countries."

The XXXXXXXXXX Member on the TTHWP confirmed that inhaled forms of salbutamol and terbutaline were available in New Zealand only as 'prescription only medicines'

although pharmacists could sell these medicines in an emergency. The New Zealand representative also noted that the proposal to schedule salbutamol for treatment of asthma as a 'pharmacist only medicine' was strongly opposed in New Zealand by doctors and asthma specialists and that this position was likely to remain unchanged. Further consideration of harmonisation of scheduling was deferred for 2 years.

In attempting to identify possible issues related to the safety of these substances, the Working Party had approached ADRAC for advice on reports of adverse drug reactions with these medicines but the reports received did not allow identification of the product formulation. Therefore it was unclear if the OTC availability of salbutamol and terbutaline aerosols and dry powder formulations for the treatment of asthma was a public health concern in Australia. However, the Working Party requested the Secretary undertake a literature review (2000 onwards) focusing principally on the safety in use of pharmacy-only aerosol and dry powdered formulations of salbutamol and terbutaline as well as access arrangements in comparable overseas countries.

## DISCUSSION

The NDPSC noted a number of articles identified by the TTHWP that highlighted improved clinical outcomes in asthma management through the involvement of pharmacists. Adverse effects associated with the use of beta agonists were not uncommon. The paper by Abramson, Walters and Walters "Adverse Effects of Beta Agonists" *Am J Respir Med* 2003; 2 pps 287-297, reported possible links between asthma related deaths (in New Zealand, Canada, Australia and the UK) and nebulised asthma medication. The study concluded that "escalating doses of beta agonists used in acute deteriorations of asthma, in the absence of proper medical management with corticosteroids and oxygen can be harmful and indeed dangerous or life threatening, particularly in the case with the use of nebulised medication. On the other hand, fears about regular use of beta-2 agonists in persistent but reasonably controlled and stable asthma seem to be largely unfounded."

The Committee noted the Working Party's advice that, in the absence of safety concerns and on the grounds of harmonisation, the NDPSC be advised that it should again recommend to the New Zealand Ministry of Health that metered aerosols and dry powdered formulations of salbutamol and terbutaline be considered for entry in Part II consistent with current Schedule 3 entries in the SUSDP.

The XXXXXXXXXX Member agreed that it was appropriate for the NDPSC to again recommend to the MCC that there be further consideration to harmonisation with the SUSDP. He noted that since the NDPSC and the MCC had last considered harmonisation in respect to salbutamol and terbutaline, there had been considerable experience by pharmacists in assisting in asthma management leading to greater confidence that Schedule 3 equivalent harmonisation in New Zealand should not result in public health concerns.

NDPSC members also noted that, while there had been early opposition to Schedule 3 classification of beta agonists, more recent reviews had endorsed the appropriateness of the wider availability of certain asthma medications through pharmacies. The NDPSC members endorsed the view expressed by the XXXXXXXXXX Member that pharmacists had demonstrated that they played an important role in asthma management.

## **OUTCOME**

The NDPSC agreed to recommend to the New Zealand Ministry of Health that on the basis of established safety in use and to achieve scheduling harmonisation, metered aerosols and dry powdered formulations of salbutamol and terbutaline be considered for entry in Part II consistent with the current Schedule 3 entries in the SUSDP.

### **1.8.2.1 PROPANTHELINE**

#### **PURPOSE**

The Committee considered the proposal to delete the Schedule 2 entry for propantheline in order to achieve harmonisation of scheduling with New Zealand.

#### **BACKGROUND**

The NDPSC 21<sup>st</sup> Meeting (May 1999) considered harmonisation of the scheduling for propantheline but agreed that the existing Schedule 4 entry in Australia remained appropriate at the time. This decision was made on the grounds that there was one existing product in Australia containing propantheline which was indicated for adjunctive therapy in the treatment of peptic ulcer, neurogenic bladder, urinary incontinence in patients with detrusor hyperactivity and hyperhidrosis.

In the context of Trans-Tasman harmonisation the TTHWP 10<sup>th</sup> Meeting (October 2003) (Item 2.3.3) reviewed the scheduling of propantheline and noted that it was listed in Schedule 4 of the SUSDP except in preparations for topical use which were Schedule 2. However, propantheline was a prescription medicine in New Zealand with no provision for a less restrictive classification. The TTHWP 10<sup>th</sup> Meeting had also noted that the oral preparation containing propantheline bromide for use as an adjunctive therapy in the treatment of peptic ulcer (gastric and duodenal), neurogenic bladder, urinary incontinence in patients with detrusor hyperactivity and hyperhidrosis was still registered in Australia. There were no other registered products for human topical use or veterinary use containing propantheline.

The Committee agreed that, as there were no topical human or veterinary preparations containing propantheline registered in Australia, harmonisation of scheduling could be achieved by deletion of the Schedule 2 entry.



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## **DISCUSSION**

The Committee noted that at the 41<sup>st</sup> meeting of NDPSC (June 2004) the Committee had agreed to foreshadow for the October 2004 meeting, the deletion of the Schedule 2 entry for propantheline. The Committee's decision had been Gazetted in the pre-meeting Gazette prior to the October 2004 meeting.

The Committee noted that there were no responses to the Gazettal of the proposal to delete the Schedule 2 entry for propantheline.

### **DECISION 2004/42 – 1**

The Committee agreed to delete the Schedule 2 entry for propantheline as the basis of scheduling harmonisation between Australia and New Zealand.

#### **Schedule 2 – Amendment**

PROPANTHELINE – delete entry.

#### **Schedule 4 - Amendment**

PROPANTHELINE – amend the entry to read

PROPANTHELINE.

### **1.8.2.2 AMPHOTERICIN**

#### **PURPOSE**

The Committee considered progress in assessing the possibility of resistance development arising from more widespread use of amphotericin should there be a relaxation in its Schedule 4 status.

#### **BACKGROUND**

The June 2004 meeting of the NDPSC recalled that the TTHWP 8<sup>th</sup> Meeting (October 2002) recommended that topical preparations containing amphotericin for the treatment of oral candidiasis be included in Schedule 3 of the SUSDP (Recommendation 8.11). This change would harmonise the scheduling with New Zealand.

The item was considered at the NDPSC 39<sup>th</sup> Meeting (October 2003). A pre-meeting submission raised the possibility that more widespread use of amphotericin could lead to the development of resistance and therefore reduced effectiveness. Further discussion was deferred to allow advice to be sought from the ADEC on the potential for resistance to

develop with topical use of amphotericin. The ADEC subsequently advised that the matter should be referred to EAGAR.

The NDPSC 40<sup>th</sup> Meeting (February 2004) agreed to refer the matter to EAGAR, noting that, should EAGAR consider that the issue was outside its terms of reference, EAGAR be asked to convene a special advisory panel to provide advice to NDPSC on the potential for resistance development with amphotericin. A decision on the harmonisation proposals was deferred pending advice from EAGAR. The Chair of EAGAR undertook to table the information provided by NDPSC at the EAGAR April 2004 meeting.

The Committee received advice that EAGAR saw the issue of potential resistance to amphotericin as being of critical importance and therefore requested that a detailed risk assessment should be compiled before further advice could be given. EAGAR recommended that there be no change in the scheduling of amphotericin pending a broad ranging review of antifungals.

The Committee noted that EAGAR had been more concerned with antibiotic resistance rather than fungal resistance. The Committee also noted that the NHMRC had recently advised that in future, EAGAR would not undertake primary reviews but would review the outcome of reviews of the potential for antibiotic resistance undertaken by regulatory authorities. As a result, an assessment of the potential for resistance development associated with more widespread use of products containing amphotericin would need to be arranged by the NDPSC and the outcome submitted to the EAGAR for review.

The Committee also noted pre-meeting advice from the XXXXXXXXXX agreeing to the placement of amphotericin topical products in Schedule 3.

The Committee agreed to defer further consideration of this matter until the NDPSC 42<sup>nd</sup> Meeting (October 2004). In the meantime the Committee requested that the Secretariat arrange for a review of amphotericin for possible resistance development arising from more widespread use should there be a relaxation of the scheduling.

## **DISCUSSION**

The Secretariat advised that it had arranged for the review of possible resistance development to be undertaken by an expert in microbiology. Literature searches had been undertaken to assist the reviewer but the review has not been able to be completed in time for the October meeting. The review would be presented to NDPSC at its February 2005 meeting.

## **OUTCOME**

The Committee agreed to consider the amphotericin report and the possibility of resistance at its February 2005 meeting.

[Item removed]

## **1.9 PROPOSED CHANGES TO THE SUSDP**

There were no items were considered.

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

### **2.1 SUSDP, PART 1**

No items were considered.

### **2.2 SUSDP, PART 2**

#### **2.2.1 LABELS AND CONTAINERS**

#### **PURPOSE**

The Committee considered comments received in relation to the proposal for the harmonisation with New Zealand of labelling requirements for Schedule 8 substances with the New Zealand *Misuse of Drugs Act*.

#### **BACKGROUND**

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

Members were advised that the labelling issue for harmonised controlled drugs had been discussed further at the June 2003 meeting of the Trans-Tasman Harmonisation Working Party. At this meeting members of the working party had agreed that the approach proposed at the October 2002 meeting may provide a way forward on the harmonisation of scheduling for controlled substances. This would be to harmonise the labelling of Schedule 8 substances whilst recognising that the differing legislative environments made harmonisation of “controlled substances” in Schedules 2, 3 and 4 unlikely in the short term.

There was general support for investigating options for Schedule 8 labelling schemes that met both Australian and New Zealand labelling requirements.

The Committee endorsed the amended decision 8/12 of the Working Party and agreed, on the grounds of partial harmonisation to foreshadow amendment of Part 2, paragraph 7(1)(a)(iv) and to recommend to the New Zealand Ministry of Health that they vary the

labelling requirement for controlled drugs included in Schedule 8 of the SUSDP to include the letters “NZ” preceding the designation for the controlled substance.

The foreshadowed amendment to Part 2 of the SUSDP was Gazetted for consideration at the October 2003 meeting. The October 2003 meeting considered this matter and agreed to drop the letters “NZ” from the proposal as their inclusion may lead to confusion and would not meet the requirements of the MODA. Additionally, the Secretariat was asked to seek comment from the pharmacy organisations. The Secretariat wrote to the XXXXXXXXXX, XXXXXXXXXX and its Branches and the XXXXXXXXXX.

## DISCUSSION

In response, comment was received from XXXXXXXXXX and the XXXXXXXXXX.

The XXXXXXXXXX indicated that its preferred option was to have the signal heading on Schedule 8 substances contain only the words “Controlled Drug”. The XXXXXXXXXX also expressed the view that the inclusion of the designation B3 could be a source of confusion for Australian pharmacists and that there was also the potential for confusion with the ADEC pregnancy-warning category.

The XXXXXXXXXX also considered that the inclusion of B3 (one of seven symbols applicable to Controlled Drugs in New Zealand) in the heading might also be confusing in Australia. The XXXXXXXXXX believed that confusion would extend to doctors and nurses.

The XXXXXXXXXX also considered that the proposal had implications for substances in other schedules and *de-facto* created a subset of the schedules that ran counter to harmonisation between the Australian States. However, the XXXXXXXXXX considered that the heading could read “CONTROLLED DRUG [(B3 in NZ] or similar. It was also suggested that a change in New Zealand laws so that the symbol B3 could be included elsewhere on the label would be consistent with approaches in other countries.

The XXXXXXXXXX Member confirmed that all medicines controlled by the MODA were required to have “CONTROLLED DRUG” on the label whereas in Australia, this was a requirement only for Schedule 8 drugs. The XXXXXXXXXX Member considered that this was a good basis for harmonisation of Schedule 8 substances even if the inclusion of the New Zealand MODA Classifications ie [B3 in NZ] or [NZ- B3] needed to be retained. The XXXXXXXXXX Member was also confident that while there might be some initial confusion over new labelling, this would be quickly overcome through pharmacist education with the cooperation of professional bodies, NZMOH and the TGA. Once explained and in use, any confusion that might arise would soon diminish.

The Committee noted that the New Zealand MODA Classification requirement could be satisfied without the need to include “NZ”. The proposed amendment to Part 2, paragraph 7 would be amended to reflect this.

## OUTCOME

The Committee agreed that, in the interests of Australia/New Zealand harmonisation, it proceed with the foreshadowed amendment to Part 2, Paragraph 7 (1)(a)(iv) as modified and agreed at the October 2003 meeting.

## FORESHADOWED DECISION (for consideration at the February 2005 meeting)

### Part 2, LABELS AND CONTAINERS

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

- (iv) if the poison:
  - (A) is a Schedule 5 poison, with nothing, other than a Class label as specified in the *Australian Code for the Transport of Dangerous Goods by Road and Rail* or a statement of the principal hazard of the poison, written on that line;
  - (B) is a Schedule 8 poison, with nothing, other than a NZ designation as specified in the *New Zealand Misuse of Drugs Act (1975)* written on that line ;
  - (C) is not a Schedule 5 or a Schedule 8 poison , with nothing, other than a Class label as specified in the *Australian Code for the Transport of Dangerous Goods by Road and Rail*, written on that line;

### 2.3 SUSDP, PART 3

No items were considered.

## **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 OCTENOL**

##### **PURPOSE**

The Committee considered further comment in relation to a cut-off to Schedule 5 for octenol.

##### **BACKGROUND**

The scheduling of octenol was considered at the June 2004 meeting in response to an application from the XXXXXXXXXX for the registration of a new product XXXXXXXXXX, containing 100% (1000 ml/L) octenol (1-Octen-3-ol, CAS 3391-86-4). Octenol will be used as an attractant, luring mosquitoes and biting midges into a trap where it is claimed that they are dehydrated and die within 24 hours. 1-Octen-3-ol is a naturally occurring compound found in plants, animals, edible fruits and vegetables. Furthermore, it is widely used as a flavouring ingredient in foods and is approved by the US FDA as a direct food additive and the Council of Europe as an artificial flavouring agent. The US FDA considers that octenol is generally recognised as safe (GRAS).

The Committee noted a recommendation from the Office of Chemical Safety (OCS) that an entry for octenol be included in Schedule 6 of the SUSDP with a cut off to Schedule 5 when packed in bite and crush resistant cartridges containing 2 g or less of octenol. The Committee agreed it was appropriate to include an entry for 1-octen-3-ol in Schedule 6 on the basis of its acute oral toxicity. However, members expressed concern that there did not appear to be a recognised standard to test whether the packaging was “bite and crush resistant” as the sponsor had claimed. The Committee agreed that the actual product packaging would need to be seen by members before any decision regarding a cut-off to Schedule 5 could be considered. As an alternative to deferring the scheduling consideration of octenol, the Committee also agreed to include an entry for the substance in Schedule 6 and then subsequently consider the proposal for a cut-off to Schedule 5 at the October 2004 meeting after examining the product’s packaging.

An example of the XXXXXXXXXX packaging was obtained from the sponsor and forwarded to the OCS for consideration.

## DISCUSSION

The Committee noted the following points raised by the OCS report for consideration:

- As octenol has an acute oral LD50 of 340mg/kg bw, the amount present in the final product, 1.66 g could be toxic to children if ingested accidentally by a child. For this reason, the applicant conducted a bite/crush resistance test on the product in which cartridges containing octenol were exposed to crushing/biting forces similar to those of a child. The results showed that the lure carrier was crush/bite resistant and the seals remained intact. Therefore, it was concluded that a child would not gain easy access to octenol in the product by chewing on the cartridge. The packaging of the cartridge within a covered PET tray should further reduce potential exposure to octenol.

The Committee noted advice regarding the use of octenol in food and cosmetics received from Food Standards Australia and New Zealand (FSANZ), the XXXXXXXXX and the XXXXXXXXX.

- Food Standards Australia and New Zealand advised that although octenol was not specifically listed as an additive within the provisions of the Code it could be used in food by virtue of clause 11 of Standard 1.3.1-Food Additives. This clause allows the use of octenol as a food additive in Australia and New Zealand because it is listed in United States Code of Federal Regulations, 1996, 21 CFR Part 172.515.
- The XXXXXXXXX advised that octenol has some limited use as a fragrance ingredient, often being used for creating a lavender scent in products such as fine fragrances, soaps and skin and hair care products at levels between 0.00001% and 0.08%.
- XXXXXXXXX advised that there was little "use" information available for octenol in cosmetics or personal care products in Australia. Member companies indicated that octenol is included in international products and expressed the desire to maintain the flexibility to use octenol locally as the substance imparts a particular type of fragrance. Furthermore, XXXXXXXXX noted the summary toxicity information on the US EPA website and the EPA's comments that: "The Agency waived the requirements for toxicity studies based on the packaging methods; small amount of the octenol that evaporates; widespread occurrence in plants, animals, and edible fruits and vegetables; approval by the US Food and Drug Administration for use in food; and status as Generally Recognized as Safe."

After a close inspection of the product provided by the sponsor, the Committee expressed the opinion that the packaging was not child-resistant and that potentially a child could gain access to a toxic quantity of octenol. Accordingly, the Committee expressed reluctance to include an entry for octenol in Schedule 5.

The Committee was of the opinion that limiting the Schedule 6 entry for octenol to a specific product was inappropriate on the basis of its acute oral toxicity and widespread

use in foods and cosmetics. Accordingly, members favoured amending Decision 2004/41 – 9 so that the Schedule 6 entry covered all uses of octenol with an appropriate exemption cut-off for use in foods and cosmetics. The XXXXXXXXXX Member suggested that a cut-off set at 5% would ensure that food, cosmetics and personal care products were not captured by the Schedule 6 entry.

#### **DECISION 2004/42 – 2 (Variation of Decision 2004/41 – 9)**

In accordance with subregulation 42ZCZ(3), the Committee agreed to vary decision 2004/41 – 9 to cover all uses and include an appropriate cut-off.

#### **Schedule 6 – New entry**

1-OCTEN-3-OL **except** in preparations containing 5 per cent or less of 1-octen-3-ol.

### **4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS**

#### **4.1 EYELASH AND EYEBROW TINTING PRODUCTS**

##### **PURPOSE**

The Committee considered the outcome of the NICNAS preliminary review of chemicals in hair dyes and an assessment of the toxicity profiles and classifications on skin/eye irritancy for paraphenylenediamine and toluenediamine.

##### **BACKGROUND**

At the February 2004 meeting, the Committee was provided with a update on the progress of investigations being separately conducted by XXXXXXXXXX and XXXXXXXXXX on incorrectly packed and labelled paraphenylenediamine and toluenediamine eyelash and eyebrow tinting and hair care products. The XXXXXXXXXX Member advised the Committee that all eyelash/eyebrow tinting products on the Australian market are imported from either Austria, Germany or Switzerland and contain similar ingredients. Consequently, XXXXXXXXXX had recommended that advice regarding this matter be sought from the XXXXXXXXXX. Additionally, the XXXXXXXXXX Member agreed to facilitate a compliance and education program with industry on the regulatory requirements under NICNAS. The Committee also considered a public submission from the XXXXXXXXXX seeking an exemption from scheduling for eyelash/eyebrow tinting products containing paraphenylenediamine and toluenediamine on the grounds that application by professional beauty therapists would minimise the risk associated with their use. The Committee was of the view that it did not have enough data to determine the potential danger posed to the eye by paraphenylenediamine and toluenediamine. Given that NICNAS was at that time in the process of conducting a review of all hair dye ingredients currently used in Australia, the Committee agreed to defer this matter to a future meeting to allow consideration of the final NICNAS review.



At the June 2004 meeting, the Committee was further updated on the progress of these investigations. The XXXXXXXXXX Member advised the Committee that XXXXXXXXXX had investigated recent claims of the inappropriate retail sale of several hair dye products. The distributors (one in XXXXXXXXXX and three in XXXXXXXXXX) were contacted and asked to remove the products from retail sale. The XXXXXXXXXX Member advised the Committee that the XXXXXXXXXX had informed companies that, until the labelling of eyelash and eyebrow tinting products issue is resolved, the XXXXXXXXXX would only allow salon use of these products. Companies were also warned that, if such a product were to be found on retail sale, action could be taken against the company. The XXXXXXXXXX Member indicated that for there to be a successful resolution to this issue the Committee would need to assess the potential for eye damage resulting from exposure to eyelash and eyebrow tinting products containing paraphenylenediamine and toluenediamine.

XXXXXXXXXX Member advised the Committee that paraphenylenediamine and toluenediamine are included in the list of permanent hair dye chemicals being reviewed in Europe and agreed to seek the toxicity profiles and classifications on skin/eye irritancy and report to the October 2004 meeting.

## DISCUSSION

The Committee noted the outcomes of the NICNAS preliminary review of chemicals in hair dyes provided by the XXXXXXXXXX Member. In particular, it was noted that NICNAS would maintain a watching brief on the activities in Europe and that consequential regulatory action would depend on the assessment outcomes.

The Committee also noted the following points raised in the NICNAS report on skin and eye irritancy for paraphenylenediamine and toluenediamine for consideration:

- Available data indicates that p-phenylenediamine is used in permanent/semi-permanent hair colour preparations in Australia and the EU. It is a skin sensitizer and a skin and eye irritant.
- Importantly, all phenylenediamines are listed in Schedule 6 of the SUSDP unless specifically labelled including an exclusion for eyebrow and eyelash treatment. In addition it is prohibited in skin colouring preparation via listing in Appendix C of the SUSDP.
- The public submission for rescheduling from the XXXXXXXXXX did not identify a particular substituted form of the chemical, however, available data indicates that p-toluenediamine is used in permanent/semi-permanent hair colour preparations in Australia and the EU. While data are not specifically available for some substituted forms of the chemical, in general, toluenediamines can be considered skin irritants, eye irritants (severe in some instances) and skin sensitizers. Data are available however, to confirm that p-toluenediamine is a severe skin and eye irritant and a skin sensitizer.

- All toluenediamines are classified as Schedule 6 poisons unless specifically labelled including an exclusion for eyebrow and eyelash treatment (see above). Toluenediamines are not listed in Appendix C of the SUSDP.
- The United States Food and Drug Administration has issued a warning against the use of "permanent" eyebrow and eyelash dyeing. The *Food, Drug and Cosmetic Act* of 1938 prohibits the marketing of hair dyes for eyelash and eyebrow tinting or dyeing because this practice has been known to cause severe eye injuries and even blindness.
- The FDA advises that consumers should be aware that there are no natural or synthetic colour additives approved by FDA for dyeing or tinting eyelashes and eyebrows – either for use in beauty salons or in the home. In fact, the law requires all hair dye products to include instructions for performing patch tests before use to identify possible allergic reactions, and to carry warnings about the dangers of applying these products to eyebrows and eyelashes.
- In the European Union, phenylenediamines are listed in Annex III Part 1 of the Cosmetics Directive (List of substances which cosmetics products must not contain except subject to restrictions and conditions laid down). For general use, the label must contain the following warning statements; "can cause allergic reaction" "Contains phenylenediamines" and "Do not use to dye eyelashes or eyebrows". For professional use the label must contain the following warning statements; "For professional use only" "Contains phenylenediamines" "Can cause an allergic reaction" and "Wear suitable gloves". The Cosmetics Directive has no specific controls for toluenediamines.
- Information available for chemicals confirmed as ingredients in permanent hair dye preparations used in Australia meet the classification criteria for S6 poisons. p-Phenylenediamine oral LD50 (rat) 80 mg/kg inhalation LD50 (rat) 920 mg/ L/4h and skin sensitiser. p-Toluenediamine oral LD50 (rat) 102 mg/kg, severe skin and eye irritant and skin sensitiser.

On the basis of the above information, the NICNAS evaluator recommended that the exemption from scheduling sought by the XXXXXXXXXX be declined. Furthermore, the evaluator recommended that the Committee consider either amending the current Schedule 6 entries for phenylenediamines and toluenediamines to mandate the current warning statement or prohibiting their use in eyelash and eyebrow tinting products through entries in Appendix C. It was noted that the current warning statement was mandatory through Appendix F Warning Statement 21.

A member informed the Committee that amending the Schedule 6 entries for phenylenediamines and toluenediamines would require all hair dye products to be labelled as POISON and have a significant regulatory impact on industry. Given there is an entry for phenylenediamines in Appendix C when in preparations for skin colouration, the member suggested that the logical way to prohibit their use in eyelash and eyebrow tinting was to expand this entry. A similar entry in Appendix C for toluenediamines could also be included. Furthermore, it was understood that entries in Appendix C would enable

the States and Territories to take regulatory action against the sale and use of these products.

## **OUTCOME**

The Committee agreed to foreshadow an amendment to the current Appendix C entry for phenylenediamines to include the prohibition on use for eyelash and eyebrow tinting. The Committee further agreed to foreshadow the inclusion of a new Appendix C entry for toluenediamines to prohibit its use in eyelash and eyebrow tinting. This action was being taken due to concerns surrounding the potential of the chemicals to cause severe eye injuries.

## **FORESHADOWED DECISION (for consideration at the February 2005 meeting)**

### **Appendix C – Amendment**

PHENYLENEDIAMINES – Amend to read:

PHENYLENEDIAMINES in preparations for skin colouration and dyeing of eyelashes or eyebrows.

### **Appendix C – New entry**

TOLUENEDIAMINE in preparations for the dyeing of eyelashes or eyebrows.

## **4.2 METHYLCYCLOPENTADIENYL MAGNESIUM TRICARBONYL**

### **PURPOSE**

The Committee considered the foreshadowed Schedule 7 entry for methylcyclopentadienyl manganese tricarbonyl (MMT).

### **BACKGROUND**

The scheduling of MMT was considered at the October 2003 meeting where it was proposed that this substance be included in Schedule 7 with a cut-off to Schedule 6 for fuel additive preparations containing 10% or less of MMT when fitted with a child-resistant closure. MMT is an anti-valve seat recession additive in automotive lead replacement petrol. MMT is also an octane enhancer. It is either pre-blended at the refinery or added to unleaded petrol by the vehicle owner and acts as a lubricating agent to prevent excessive valve seat wear and recession of the valve seat into the automotive cylinder head.

The Committee based its decision on the acute toxicological profile of MMT and that the use pattern of consumer products fitted with a child-resistant closure would limit the exposure direct to the public. The scheduling of MMT was considered following the

completion of a Priority Existing Chemical (PEC) Assessment Report by NICNAS. The October 2003 meeting noted that the companies producing MMT products who had provided information to NICNAS for assessment had not taken the opportunity to make a submission to the NDPSC with regard to the scheduling of MMT. The Committee agreed to foreshadow the proposed scheduling of MMT to allow interested parties to comment prior to a decision being made.

At the February 2004 meeting, a number of public submissions were received from companies and industry groups involved in the importation, reformulation and manufacture of MMT or products containing the substance. However, the consensus of opinion regarding the foreshadowed scheduling proposal was that industry had not had sufficient time to fully assess the regulatory and commercial impact of the Committee's decision. Consequently, Committee deferred the matter to allow for an adequate assessment of the implications resulting from the scheduling decision to be completed.

At the June 2004 Meeting, the Committee noted that the consensus of opinion from industry was that the scheduling of MMT for industrial use was unnecessary and would result in limited public health benefits. Furthermore, the inclusion of MMT in Schedule 7 would subject industrial users to additional regulatory burden. Given that the scheduling was targeted at the regulation of consumer sized containers, industry was of the view that an exemption from the requirements of scheduling was appropriate for industrial use and may be achieved through a pack size limit. It was proposed by XXXXXXXXXX and others that MMT and all preparations containing MMT be exempt from the requirements of scheduling when in pack sizes greater than 20 litres or when used in laboratory analysis. For pack sizes less than 20 litres, MMT be included in Schedule 7 with a cut-off to Schedule 6 for preparations containing 10% or less and a cut-off to Schedule 5 for preparations containing 5% or less when fitted with a child-resistant closure. The Committee was advised that several jurisdictions had the capacity to allow exemptions for the industrial use of Schedule 7 substances through their respective legislation. The Committee did not consider it appropriate to exempt a Schedule 7 poison from the requirements of scheduling for industrial use on the basis of pack size, particularly when there is a mechanism in place to exempt industrial use through State and Territory legislation. The Jurisdictions were asked to advise the Secretariat of the requirements for industrial use exemptions in each State and Territory with a view to providing this information to the companies that import MMT or manufacture products containing the substance. Furthermore, the Committee did not agree that a further cut-off to Schedule 5 for preparations containing 5% or less of MMT was warranted in the absence of specific toxicological data.

Whilst the Committee appreciated the concerns raised by industry, Members were of the view that the inclusion of MMT in Schedule 7 with a cut-off to Schedule 6 for fuel additive preparations containing 10% or less was justified on the basis of its toxicological profile. The Committee was forced to foreshadow the decision as the consideration of scheduling was not included in the June 2004 pre-meeting gazette.

## **DISCUSSION**

The Committee noted that information regarding industrial use exemptions in each State and Territory had been provided to those who made June 2004 pre-meeting submissions. The Committee further noted that the majority of Jurisdictions still require licenses for the supply and sale of Schedule 7 poisons.

The Committee was informed that public submissions had been received from XXXXXXXXXX and the XXXXXXXXXX. Members were advised that XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX also made submissions to the October 2004 meeting, however, these were received after the closing date. Industry expressed disappointment at the Committee's decision to include MMT in Schedule 7 without a general exemption for industrial use based on pack size. Accordingly, industry asked that the Committee reconsider its decision taking into account their submissions to the June 2004 meeting.

Members were sympathetic to the inadvertent impact on industry resulting from the proposed inclusion of MMT in Schedule 7. However, the Committee was of the view that a general exemption through Appendix A would be inappropriate opting for an exemption from the Schedule 7 entry to address industry's concerns. Members also expressed concern that a pack size limit of 20 L may not preclude the use of MMT to purely non-domestic use. Accordingly, this value was increased to 100 L.

## **DECISION 2004/42 – 3**

The Committee agreed to include methylcyclopentadienyl manganese tricarbonyl in Schedule 7 with a cut-off to Schedule 6 at 10%. Furthermore, the Committee agreed to exempt MMT from the requirements of scheduling when packed in containers having a nominal capacity of 100 L or more.

### **Schedule 7 – New Entry**

METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL **except:**

- (a) when included in Schedule 6;
- (b) when used in laboratory analysis; or
- (c) when packed for industrial use in containers with a nominal capacity of 100 L or more.

### **Schedule 6 – New Entry**

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

### **4.3 CREOSOTE**

#### **PURPOSE**

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

#### **BACKGROUND**

The June 2003 meeting agreed to ask the Office of Chemical Safety (OCS) to review the safety of creosote(s) derived from coal. This request was based upon concerns being raised about the carcinogenic potential of creosote and safety for use as a wood preservative. At the June 2003 meeting, the Committee considered an overview of the draft IPCS CICAD on creosote(s) derived from coal prepared by the OCS. The Committee was asked to consider:

- The creation of a specific SUSDP entry for creosote(s) derived from coal, with entries if and as necessary for other coal tar derived mixtures, and wood creosote.
- Whether the marketing of creosote(s) derived from coal as a wood preservative should be limited to industrial use and to licensed applicators.
- Whether all marketed creosote preparations should be required to contain limits on specific toxic and carcinogenic contaminants of concern (eg. less than 0.005% by weight of benzo[a]pyrene and water-extractable phenols at less than 3% by weight).
- The appropriateness of creosote(s) preparations derived from coal being available for the treatment of psoriasis (and for any other cosmetic uses that may exist).
- The appropriateness of creosote being available in oral pharmaceutical preparations.

At the October 2003 meeting, the Committee asked that advice be sought from the APVMA, MEC and CMEC regarding the potential impact on existing products should creosote and related substances be scheduled. This advice was provided to the February 2004 meeting for the Committee consideration.

The APVMA advised that there were 10 products containing creosote registered by the APVMA at the time. The majority (7) were for the treatment of timber and timber products, but there was also a farm disinfectant product, a liniment product and an anti-fouling paint registered containing creosote with concentrations ranging between 43 g/L to 1044 g/L. In addition to these products, there were another 11 products containing coal tar or tar acids. These products are registered for use as dog and cat washes, equine grooming aids, ointments, disinfectants and blowfly strike treatments with concentrations ranging between 3 g/L to 419 g/L.

The Medicines Evaluation Committee (MEC) highlighted the following for consideration:

- The ARTG includes products containing ‘creosote’, coal tar, ‘tar’ (pine tar) and cade oil (juniper tar).
- None of the products containing ‘creosote’ have been evaluated by the TGA; most are listed and most appear to be indicated for use as expectorants/decongestants for coughs;
- All the Australian products containing coal tar are registered, with most of the evaluated products indicated for itchy skin and/or scalp conditions (eg. psoriasis, seborrhoeic dermatitis, seborrhoea, dandruff, eczema, dermatitis) – ie. conditions consistent with those accepted by the ARGOM policy guideline on ‘Coal tar preparations’;
- At least two of the ‘grandfathered’ products containing coal tar are indicated for nappy rash – ie. these products do not comply with the ARGOM guideline;
- Most of the evaluated registered products containing pine tar are indicated for use on itchy and/or inflamed skin (eg. dermatitis, eczema, dry skin, nappy rash, psoriasis);
- Most of the products containing cade oil are ‘grandfathered’ – all the registered products are intended for inflamed skin/scalp conditions; and
- A number of the products contain more than one tar.

The Office of Complementary Medicines (OCM) advised that, as creosote is regulated as an over-the-counter registrable, they are unable to provide comment.

The Committee expressed concern that there appeared to be no uniformity in the use of the terms “creosote”, “wood creosote”, “coal tar creosote” and “coal tar BP”. Similarly, the type of the creosote present in the registered and listed medicines identified by the MEC and the products registered by the APVMA were also poorly defined. Accordingly, the Committee asked that the nature and percentage of the creosote present in the registered and listed medicines and agricultural and veterinary products be determined in consultation with the TGA and the APVMA and that “coal tar creosote” be clearly defined. The Committee deferred its consideration of creosote to the June 2004 meeting to allow further information and advice to be obtained.

At the June 2004 meeting the Committee noted that advice received from the APVMA and the OTC Medicines Section of the TGA.

The APVMA provided the information it had available on the specifications and chemical composition of the coal derivative/s in certain agricultural and veterinary products and advised that:

- Approximately half of the products containing creosote, coal tar and tar acids (and synonyms) were registered under previous State-based registration systems and that the APVMA did not hold detailed chemical specifications of the coal derivatives.
- In a number of cases, general information on the nature of the coal derivative is available (eg. complies with a particular Australian Standard or pharmacopeial

monograph). However in some cases, the cited pharmacopeial monographs are out of date.

- Information regarding composition and general specifications were found for some coal derived active constituents. However, detailed chemical specifications and CAS numbers were generally not available.

The OTC Medicines Section of the TGA advised that the AAN 'creosote' refers to creosote as defined by Martindale - ie. wood creosote. Therefore, all products stated as containing creosote should contain wood creosote. The five registered products containing creosote identified in their previous advice were “grandfathered” and have not been evaluated by the TGA. As such, no information is available on these products, and the type of creosote present has never been required to be characterised. Four of these products would be regulated by the OTC Medicines Section if marketed and the fifth registered product (also “grandfathered”) would be regulated by the Office of Complementary Medicines (OCM). The listed products containing creosote for supply in Australia are the responsibility of the OCM and, as such, further information would need to be obtained on those products from them.

The OTC Medicines Section further advised that the TGA requires coal tar (any relevant AAN) or tar (ie. pine tar) in registered products to meet the requirements of the BP monographs for 'Coal tar' or 'Tar', respectively. No further information is currently available on products containing tars, as the OTC Medicines Section has not evaluated any of these products.

The Committee expressed disappointment that more information could not be gathered on the nature of the creosote present in the “grandfathered” products identified by the TGA.

A member advised the Committee that MEC had recently reviewed their guidelines on coal tar and that this involved extensive consultation with industry. The member suggested that perhaps the Committee could seek advice from MEC on this matter. The Committee agreed to seek the MEC coal tar guidelines for consideration at the October 2004 meeting.

Members agreed that the way forward was to publish in the Gazette the Committee's intention to include entries for creosote derived from coal and creosote derived from beechwood in Schedule 7 of the SUSDP on the basis of their toxicity and carcinogenic characteristics. The Committee would also redefine the current creosote entries in Schedules 2 and 6 to specify creosote derived from wood other than beechwood. It was hoped that in doing so sponsors of human therapeutic and veterinary products, particularly those “grandfathered” into their respective regulatory schemes, would be encouraged to provide data on the nature of the creosote present thus allowing the Committee to draft schedule entries for these creosotes and to set cut-offs where appropriate.



## **DISCUSSION**

The Committee noted that a submission was received from the APVMA. The APVMA advised that companies holding registrations for products listed as containing creosote, coal tar and tar acids (and synonyms) were advised of the Committee's scheduling proposal regarding creosote. Of the 27 products identified by the APVMA to contain creosote or similar compounds, responses to the request for additional information was received from the sponsors of 14 products. In the case of four of the products (31127, 39565, 45302 and 47346), the companies no longer stocked or sold the product and thus did not provide information. For the remaining 10 products, companies submitted information such as CAS numbers, certificates of analysis, MSDS and specification sheets for the product. The APVMA Member advised that no comments regarding the scheduling proposal were received.

The Committee also noted that the MEC provided the ARGOM guideline on coal tar preparations amended 13 February 2004 for the committee's information. MEC further advised that there is no specific assessment document relating to the current coal tar preparations guideline.

The Committee was informed that the scheduling consideration of creosote was included in the pre-October 2004 meeting gazette notice and no public submissions were received from industry or the manufacturers of creosote containing products.

## **DECISION 2004/42 – 4**

The Committee agreed to include creosotes derived from coal and beechwood in Schedule 7 of the SUSDP on the basis of their toxicity and carcinogenic characteristics.

### **Schedule 7 – New entry**

CREOSOTE derived from coal.

CREOSOTE derived from beechwood.

### **Schedule 6 – Amendment**

CREOSOTE – amend entry to read:

CREOSOTE derived from wood other than beechwood **except**:

- (a) when included in Schedule 2;
- (b) in preparations for human therapeutic use containing 10 per cent or less of creosote (derived from wood other than beechwood); or

- (c) in other preparations containing 3 per cent or less of phenols and homologues of phenol boiling below 220°C.

## **Schedule 2 – Amendment**

CREOSOTE – amend entry to read:

CREOSOTE derived from wood other than beechwood for human therapeutic use,  
**except** in preparations containing 10 per cent or less of creosote derived from wood other than beechwood.

## **4.4 ALKALINE SALTS**

### **PURPOSE**

The Committee considered the scheduling of alkaline salts.

### **BACKGROUND**

The February 2004 meeting considered a review of alkaline salts by the XXXXXXXXX. The review addressed issues relating to alkaline salts, including the cut-off pH for scheduling, total alkalinity, the concentration at which the pH of a product should be measured, and the greater accessibility of automatic dishwasher detergents compared with laundry detergents in the home.

The review proposed the following options with regard to the scheduling of alkaline salts:

- Change the cut-off pH for inclusion in Schedule 5 to “more than 11.0”;
- Take the alkali reserve into account, as well as the pH, in determining whether a product is scheduled;
- Specify performance criteria when considering the scheduling of products containing alkaline salts, eg. results of Draize test, OECD test methods 404 (skin irritation), 405 (eye irritation);
- Have a subcategory in Schedule 5 for irritant products; and
- Change the concentration at which the pH is measured for scheduling purposes to 50% for laundry detergent (if the pH of a 50% solution can be accurately measured, otherwise measure the pH of a 25% solution).

Members were of the view that there was insufficient information to consider amending the Schedule 5 entry for alkaline salts in accordance with the options presented by the XXXXXXXXXX report. Accordingly, the Committee asked that more information be obtained by NICNAS on the control of similar substances in the US, Canada, NZ and Europe and in particular the way the issue of irritancy is addressed.

At the June 2004 meeting, the Committee noted a NICNAS review of the international regulation of alkaline salts. Members were of the view that to reduce the current pH cut-off for alkaline salts in Schedule 5 to pH 11 the Committee would need to know the number of products currently marketed with a pH between 11 and 11.5 and the number of harmful exposures attributed to the use of these products. Accordingly, the Committee asked that the XXXXXXXXXX Member determine the number of products currently on the Australian market with a pH between 11 and 11.5 and that the XXXXXXXXXX and XXXXXXXXXX Members seek from their respective Poisons Information Centres information regarding the number of poisonings attributed to these products and the identity of the products involved. The Members were asked to report to the October 2004 meeting.

## DISCUSSION

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

XXXXXXX advised that they have an interest in alkaline salts and sought involvement in the review process.

XXXXXXX expressed concern that:

- Several of their products are based on global formulations and would require reformulation, at significant cost, should the Committee decide to reduce the pH cut-off to 11.
- No evidence has been tabled to justify a change in scheduling of alkaline salts. The company indicates that there has not been an increase in accidental ingestions according to their Consumer Relations Department.
- The pH 11 cut-off is inconsistent with the criteria used in other countries reviewed by NICNAS and appears to be arbitrary with little connection to human safety data. Identical products do not require mandatory labelling statements in New Zealand and Europe and a change to the pH cut-off will hinder pack harmonisation for exported products, thus adding additional costs.
- Laundry detergents should not be categorised with automatic dishwashing detergents for scheduling purposes as the former is less likely to cause poisonings around the home due to reduced accessibility and is less alkaline, both in terms of alkaline reserve and pH.

The XXXXXXXXXX submission reiterated many of the concerns expressed in the XXXXXXXXXX submission.

XXXXXXX advised that a change to the scheduling of alkaline salts would have an impact to labelling, packaging, and presentation.

Members noted information provided by the XXXXXXXXXX and XXXXXXXXXX Members regarding poisonings involving detergents from the WA Poisons Information Centre (WA PIC). The members advised that:

- The data were collected from the WA PIC which services Western Australia, South Australia and the Northern Territory and the search terms used (on the “centre agent”) were Detergents – cationic, Detergents and soaps – anionic and non-ionic, Sodium carbonate, Sodium hydroxide, Potassium hydroxide, Caustic Alkali – other. It should be noted that the search strategy used may have potentially missed some product exposures by not including all the alkaline salts eg. sodium tripolyphosphate, metasilicates etc. Although the search strategy used picked up some laundry detergents and automatic dishwasher detergents there were quite a number of irrelevant products such as shampoos and dishwashing detergents captured. Also many of the poisonings were either with products such as oven cleaners and drain cleaners which are generally Schedule 5 products or with industrial alkalis. More relevant data may be obtained by prospective data collection specifically based around the alkaline salts as defined in the SUSDP.
- For the detergents and soaps categories, the total calls for the 12 month period was 756 or approximately 1 call per 4900 persons per year. Of these, 65 calls related to laundry powders/liquids and automatic dishwasher products.
- Almost all calls relating to laundry powders/liquids and automatic dishwasher products were classed as “minor” in severity with only 5 in the moderate category (symptom details listed below). However, the severity category is the severity at the time of the call and the categorization of severity is made on the basis of the information offered by the caller at the time of the call, which in most cases will be the parent of the poisoning case. Also, the data collected by the WA PIC does not include any OUTCOME data either in terms of evolving symptomatology, adverse sequel or subsequent hospitalisation or other medical treatment. This is potentially a deficiency when interpreting the data with respect to the true toxicity of the products represented and the collection of prospective data would be recommended to more truly evaluate the toxicity of alkaline laundry and automatic dishwasher products. Symptoms reported included lacrimation, conjunctival irritation, nausea, vomiting, oropharyngeal irritation/pharyngitis, other respirator symptoms, blurred vision, generalized aches/pains, glossitis, salivation, abdominal pain, other eye, ear & nose symptoms, cough/choking, hives/welts, pruritis, rhinitis, skin irritation, other GI symptoms, erythema, local skin oedema, bleeding, rash, local pain, corneal abrasion/ulceration, headache, anorexia, and dysphagia. In each case between 1 and 4 symptoms were recorded. All except two calls were classed as unintentional exposures. The other two calls related to other adverse events from cutaneous exposure. There were 29 cases where ingestion was involved, 21 ocular exposures, 9 cutaneous exposures, 4 nasal exposures, 2 inhalation exposures and 1 otic/aural exposure. Note: more than 1 exposure route involved in a number of cases.
- Of the calls relating to all detergents and soaps, only 3% of cases had symptoms of a severity greater than minor ie. moderate, severe or fatal at the time of the call. For

other alkalis, this figure was higher at 14.5% of all cases. Overall, only 7% of calls were for symptoms of a severity more than minor.

- The age groups involved were: infants (2), toddlers (42), children (5), adolescents (2), adults (10) and the age of 4 poisoning subjects was not recorded.
- In the household cleaning product categories, the symptoms reported for cases with moderate or severe symptoms included nausea, vomiting, lacrimation, blurred vision, conjunctival irritation, cough/choking, corneal abrasion/ulceration, blindness, skin erythema and irritation, laryngitis, pharyngitis, oropharyngeal irritation, abdominal pain, hyperperistalsis, diarrhoea, oesophageal injury/ulceration (severe, intentional poisoning), syncope, rhinitis, superficial burns, dyspnoea, skin blisters. In each case between 1 and 5 symptoms were recorded.
- For those cases where laundry powders and other household cleaning products caused moderate injury or worse, the symptoms involved where specific branded products were recorded were as follows:

➤ Laundry Powders/Liquids:

XXXXXXXXXX: Ingestion, vomiting, XXXXXXXXXXXX: conjunctival irritation, blurred vision, corneal abrasion/ulceration, XXXXXXXXXXXX: Ingestion, vomiting, salivation, skin erythema, XXXXXXXXXXXX: Ingestion, coughing/choking, anorexia, dysphagia, salivation, XXXXXXXXXXXX (in water): Ingestion, coughing/choking

➤ Other Household Cleaning Products:

XXXXXXXXXX: Listed with “??”, ingestion, cough/choking, laryngitis, oropharyngeal irritation, other respiratory (not precisely specified), behavioural change, XXXXXXXXXXXX: Inhalation, syncope, XXXXXXXXXXXX: Cutaneous exposure, erythema, dermal irritation, rash, other dermatologic (not precisely specified), XXXXXXXXXXXX: Intentional ingestion, oesophageal injury/ulceration, XXXXXXXXXXXX (?domestic): Ocular exposure, blurred vision, conjunctival irritation, other eye, ear & nose, XXXXXXXXXXXX: Ocular, cutaneous, inhalation, ingestion, cough/choking, conjunctival irritation, local oedema, vomiting, rhinitis, XXXXXXXXXXXX: Inhalation exposure, other respiratory, oesophageal irritation/oesophagitis, XXXXXXXXXXXX: Cutaneous exposure, blisters, erythema, irritation, local oedema, XXXXXXXXXXXX: Ocular exposure, conjunctival irritation, XXXXXXXXXXXX: Ocular exposure, corneal abrasion/ulceration, XXXXXXXXXXXX: Cutaneous, ocular exposure, conjunctival irritation, superficial burns, erythema

The XXXXXXXXXXXX Member reiterated the concerns expressed by industry, advising the Committee that there would be a significant impact on manufacturers because many of these products are marketed globally and a change to the pH cut-off would require changes to product formulations.

Members noted that the information presented did not clearly characterise products that caused a poisoning into those with a pH between 11 and 11.5 and those with a pH above 11.5. Accordingly, members were of the view that there did not appear to be evidence to

justify a change to the cut-off pH for inclusion in Schedule 5 for alkaline salts at this time.

## **OUTCOME**

The Committee agreed the current schedule of alkaline salts remained appropriate.

### **4.5 FLUMICLORAC PENTYL**

#### **PURPOSE**

The Committee further considered the scheduling of flumiclorac pentyl.

#### **BACKGROUND**

At the June 2004 meeting, the Committee considered a submission from XXXXXXXXXX for the scheduling of the new active, flumiclorac pentyl for use in XXXXXXXXXX. The product will contain 100 g/L flumiclorac pentyl as the active ingredient in a formulation containing hydrocarbon solvent. Flumiclorac pentyl is a N-phenylimide herbicide and a porphyrin biosynthesis pathway inhibitor, proposed to act by reducing the enzyme activity of protoporphyrinogen oxidase. The product is an emulsifiable concentrate and will be used as a defoliant in cotton plants.

The Committee noted the OCS evaluation report which recommended, based on the data provided, that flumiclorac pentyl be exempt from the requirements of scheduling. However, a member expressed the opinion that the data presented by the company was deficient in information regarding flumiclorac pentyl's primary mode of action in biosynthesis. In particular, concern was expressed that protoporphyrinogen oxidase is the penultimate enzyme in both chlorophyll and heme biosynthesis and should a susceptible person to porphyria come in contact with flumiclorac pentyl, it may trigger an attack. The OCS evaluator informed members that the assessment did not identify any significant haematological concerns in the mammalian studies evaluated and that this may result from flumiclorac pentyl exhibiting a greater plant specificity than other analogues previously considered by the Committee. The member acknowledged that flumiclorac pentyl did exhibit a lower toxicity profile and produced less porphyrin when compared with other compounds in its class, however, in the member's view the sponsor failed to supply data on this matter for the Committee's consideration.

A member noted that flumiclorac pentyl had been identified as a potential skin sensitiser on the basis of tests conducted in the late 1980's and early 1990's. The member was concerned that perhaps there may be more recent experiences since 1992 with the substances's skin sensitiser potential that have not been made available to the Committee for consideration. The OCS evaluator advised the Committee that, given the time lag between product registration and product sale, there was unlikely to be any significant exposure and epidemiological monitoring to produce such information. Furthermore, the evaluator reminded the Committee that the sponsor is obliged to provide all known data

to the OCS for evaluation including any monitoring data. However, in this case the sponsor had indicated that there were no findings to report. The XXXXXXXXXX Member advised the Committee that flumiclorac pentyl would be considered to be a skin sensitiser in the workplace on the basis of the tests submitted.

The Committee agreed to defer consideration of the scheduling of flumiclorac pentyl in order to seek more information regarding porphyrin metabolism and its potential to trigger an attack of porphyria. Furthermore, the Committee asked that the sponsor confirm that there is no evidence of skin sensitisation or the onset of acute porphyric attacks associated with the use of flumiclorac pentyl.

## **DISCUSSION**

The Committee noted that the sponsor provided information regarding porphyrin metabolism and the potential for flumiclorac pentyl to promote acute porphyric attacks and that this data was evaluated by the OCS.

The Committee noted the following points raised in the OCS response for consideration:

[paragraphs removed]

Based on the data above, the OCS recommended that flumiclorac pentyl be exempt from the requirements of scheduling.

An expert member advised the Committee that porphyria is not a condition that is readily diagnosed until an attack occurs and is not necessarily recognised as a hereditary condition. Given this, a Schedule 7 entry for flumiclorac pentyl was warranted despite it exhibiting relatively weak inhibitory activity for PPO in mammals.

Another member expressed the opinion that the risk the Committee needed to manage was to a very sensitive but small subset of the population and that restricting the availability of flumiclorac pentyl to this group via a Schedule 7 entry was inappropriate. The member thought that an entry for flumiclorac pentyl could be included in a less restrictive schedule and an appropriate warning that contact with the substance may trigger an acute porphyric attack be addressed through an appropriate label warning statement.

The OCS evaluator reminded that Committee that an entry for quincolorac, a substance with a similar mode of biochemical action to flumiclorac pentyl, was included in Schedule 5 at June 2004 meeting. Furthermore, the Committee had included substances in less restrictive schedules in the past on the condition that certain warning statements were included on the product label.

Members were also reminded that flumiclorac pentyl is a very slight, transient eye irritant and a potential skin sensitiser.

## **DECISION 2004/42 – 5**

The Committee agreed to include an entry for flumiclorac pentyl in Schedule 5 on the basis of its potential to trigger an acute porphyric attack and its skin sensitisation potential.

### **Schedule 5 - New entry**

FLUMICLORAC PENTYL.

## **4.6 PERMETHRIN**

### **PURPOSE**

The Committee considered post-meeting comment regarding the scheduling of permethrin.

### **BACKGROUND**

At the June 2004 meeting, XXXXXXXXXX sought the registration of a product XXXXXXXXXX for dogs (0.4 - 4 mL tubes to treat dogs of various body weights) containing two active constituents, permethrin (500 g/L, cis:trans isomers 40:60) and imidacloprid (100 g/L). The applicant proposed a change to the scheduling for permethrin to allow inclusion in Schedule 5 when packed in single use containers having a capacity of 4 mL or less. Currently, the product would be labelled as a Schedule 6 poison on the basis of its permethrin content.

XXXXXXX is intended for home use on dogs for application (up to 8 mL) on the skin every two weeks for the control of paralysis ticks (*Ixodes holocyclus*) or monthly for the control of all other ticks and/or fleas, and for mosquitoes and midges.

Based on the acute toxicity profile of XXXXXXXXXX, the Office of Chemical Safety (OCS) recommended a Schedule 5 entry for preparations containing 26-50% permethrin when packed in single use containers having a capacity of 4 mL or less.

In a public submission to the Committee, XXXXXXXXXX expressed concern that non-target species would be exposed to the substance through contact with dogs and product misuse. Therefore, XXXXXXXXXX recommended that permethrin remain in Schedule 6 and that the Committee consider lowering the 25% cut-off to Schedule 5. The Committee was advised that the submission was forwarded to the OCS for assessment. In response, the OCS advised the Committee that while there are genuine concerns, the issues identified primarily relates to off label use or inappropriate use and as such were an issue for the APVMA to consider during deliberations on label directions. The OCS expressed a view that scheduling was not an appropriate mechanism for controlling the use of products in contravention of the label directions. However, a member expressed concern over the possibility of exposure to non-target animals such as cats, not only through off



label use but also through exposure to treated dogs in the same household. The member advised the Committee that while permethrin is non-toxic to dogs at the dosage rates recommended by the sponsor, it is extremely toxic to cats at the same levels. The member considered it inappropriate to remove the “POISON” signal heading through down-scheduling the sponsor’s product because the consumer should be made aware of the risks to non-target animals such as cats.

A member also highlighted the issue of accidental ingestion by children. Specifically, the statement in the OCS report referring to a child safety study in which up to 19% of children successfully opened the product packaging and thereby could ingest the contents. The member expressed the opinion that ingestion of the product by a child may result in exposure to permethrin approaching a possibly toxic level and that moving a product such as this into Schedule 5 was inappropriate.

The Committee noted that the OCS assessment reported a child safety study which indicated that a significant proportion of children could gain access to the sponsor’s product packaging and thus potentially ingest the contents. The Committee was concerned that agreeing to the company’s request to increase the Schedule 5 cut-off for permethrin to 50% would result in the product being more readily available in homes and thus increasing the potential for permethrin exposure to children. Similarly, members were concerned that a change to the Schedule 5 entry for permethrin in accordance with the company’s proposal may also result in an increase in the poisoning of non-target species such as companion animals. Accordingly, the Committee agreed that the current scheduling of permethrin remained appropriate.

In light of the Committee’s decision, the OCS evaluator drew to the attention of members that there were products currently labelled as Schedule 5 containing 25% or less of permethrin in pack sizes with a volume of much greater than 4 mL that would pose a greater risk of exposure if accessed by children. The Committee acknowledged that there appeared to be an inconsistency in the approach to the scheduling of these products given their decision regarding the sponsor’s product and asked the Secretariat to review the existing Schedule 5 entry for permethrin including listed products and report to the October 2004.

## DISCUSSION

The Committee was informed that XXXXXXXXX submitted highlighting two issues it wished the Committee to consider in regard to the decision made at the February 2004 meeting:

- **Toxicity to Non-Target Species:** XXXXXXXXX is aware of the danger the product presents to cats and has submitted strong labelling to warn against application to cats or close contact between cats with treated dogs. During the 18 months that XXXXXXXXX has been on the market in the US, 339 direct exposures to cats have been reported to January 2004. Of these 8 animals have died, with the majority of exposed cats recovering under various unrecorded forms of treatment.

- Increased Exposure to Children in the Home: The Company disagrees with the premise that a down-scheduling of the product will make it more readily available in the home and thus increase the potential for exposure of the product to children. XXXXXXXXXX advised that the product would only be distributed through veterinarians. Additionally, market research with a similar product, XXXXXXXXXX, has shown that veterinarians are unlikely to increase the amounts of a product supplied after that product is down-schedule because their primary concern is product efficacy. Furthermore, consumers expect insecticides to be “poisonous” and treat them as such irrespective of whether the product is labelled as a Schedule 5 or Schedule 6 product. Consequently, the penetration into homes, use and storage of these products will not significantly differ.

The sponsor indicated in its submission that it is aware that the two issues identified above may counter their own argument supporting the down scheduling, however, the company believes that the scheduling of the product should primarily be based on toxicity of the formulation. Consequently, the sponsor asks that the Committee reconsider its decision.

The Committee noted that an entry in Schedule 5 would not limit the sale or supply of this product to veterinarians.

Members were reminded that the OCS evaluation presented to the June 2004 meeting advised that:

- The sponsor’s product, XXXXXXXXXX, is presented as a solution (0.4, 1.0, 2.5 or 4.0 mL) for direct application to the skin. It is packaged in a single-dose, polypropylene tube (with a child resistant polypropylene cap) rendered opaque by titanium oxide. The tubes are packed into PVC blister trays (3 or 6 wells) and sealed against aluminium foil.
- [paragraph removed]
- Based on the acute toxicity profile of the product, the OCS recommend that the Schedule 5 entry be amended to allow preparations containing 26-50% permethrin when packed in single use containers having a capacity of 4 mL or less.

In regard to the proposed Schedule 5 review, the Committee noted that the APVMA submitted a list identifying 229 agricultural and veterinary products containing permethrin currently labelled as Schedule 5 products. Of these, 178 products contain 10% or less of permethrin, 41 products contain between 10 and 15% permethrin and 5 products contain between 15 and 25% permethrin. 5 Products were identified containing greater than 25% permethrin and, as such, should be labelled as Schedule 6 products. For the purposes of the comparison of the Schedule 5 products containing permethrin and their potential exposure to children, all products in containers greater than 5 kg or 5 L were excluded. Also removed from consideration were products where the presentation would not allow easy access to the substance (eg. flea collars, flea bombs etc).

Members noted that the following assumptions were also made when calculating the dose of permethrin per swallow and percentage of LD50:

- The average volume of a swallow and weight for a small child are 5 mL and 10 kg, respectively.
- The acute oral toxicity (LD50) of permethrin used for the calculations is  $\geq 490$  mg/kg (mice). This value was taken from the OCS evaluation report for XXXXXXXXXX presented to the June 2004 meeting.

A total of 144 products remained for evaluation. So if a child were to gain access to these products and ingest 5 mL or 5g of any product, 139 of the 144 products would contain enough permethrin to achieve 11.5% or less of a LD50 dose. Of the remaining 5, one contains 20.8%, while the other 4 contain 26% of the LD50 dose in 5 mL/g. By comparison, the sponsor's product, XXXXXXXXXX, contains 44% (w/v) permethrin in a pack size of 4 mL which equates to 36% of the LD50 dose should a child ingest the contents of the tube. Therefore for the products containing 15%, 20% and 25% permethrin, a child would need to ingest approximately 33 mL (~6.5 swallows), 24.5 mL (~5 swallows) and 20 mL (~4 swallows), respectively to obtain the LD50 dose of 490 mg/kg. By comparison, for a product containing 50% permethrin, the amount required to be ingested to achieve the LD50 dose is 9.8 mL (~2 swallows).

An expert member submitted the following comments for the Committee's consideration regarding the sponsor's comments:

- The acute oral toxicity profile of permethrin (40:60 cis: trans isomers) for the mouse is  $\geq 490$  mg/kg and  $\geq 806$  mg/kg for rats which of course effectively places the active in Schedule 6. The toxicity of permethrin (and other pyrethroids) is vehicle dependent in that the compound is much more toxic by the oral route when dissolved in an organic solvent than it is when ingested as a suspension in an aqueous vehicle.
- The product under consideration XXXXXXXXXX is claimed to have an oral LD50 in excess of 2000mg/kg based on a comparison with similarly formulated products. XXXXXXXXXX was used as a solvent in the formulation. On the basis of an LD50 of about 800mg/kg in the rat for pure permethrin, a 50% preparation of permethrin should have an LD50 of about 1600 mg/kg if the same vehicle was used. This again would place such a dilution of permethrin in Schedule 6.
- On purely toxicological grounds the present product XXXXXXXXXX could well be accommodated in Schedule 5 as even if a 4ml container full was consumed by a child, harm would be unlikely to occur as the toxicity of the product was in excess of 2000 mg/kg notwithstanding the fact that it contained 50% permethrin.
- According to the OCS report to NDPSC 41, the permethrin product under consideration contains about 48% of XXXXXXXXXX (as solvent). This solvent is well known as a severe eye irritant and for this reason permethrin in this formulation can justifiably be included in S6 in spite of the fact that the oral toxicity is comparatively low. The finding that about 20% of young children can break open the

container even though it has a CRC makes the product a hazard for children in relation to eye injury.

- A point made by one correspondent was that the product did not need to be labelled “poison” because the public considers all pesticides to be poisons and consequently took all reasonable care not to get exposed to them. It is my belief that members of the public do not read labels on most pesticide products for the home, and believe that if the product is promoted for use in the domestic environment, it must be safe. Therefore, if we as a committee identify a hazard such as severe eye irritation due to the solvent in this case, we should warn the domestic users that this can occur and the way to do it is to write POISON on the label.
- In summary, I support the decision to regard this product as Schedule 6 as per current scheduling. Because of the complexity of hazard identification in relation to existing products which is related to the formulation, there is no rational basis at present for changing the existing schedules for permethrin.

The XXXXXXXXXX Member expressed the opinion that, on the basis of the toxicity exhibited, the Schedule 5 entry for permethrin should be amended to allow XXXXXXXXXX to be labelled as a Schedule 5 product.

A member noted that the toxicity data presented for consideration was not obtained on the product XXXXXXXXXX. The member sought assurances that the surrogate data was an accurate reflection of the toxicity of the product being considered. The evaluator advised the member that the “similar product” on which the toxicity data was obtained consisted of an approximately 42% solution of permethrin in XXXXXXXXXX and was expected to have a similar toxicological profile to XXXXXXXXXX. On that basis, a member suggested that perhaps a 50% solution of permethrin could be accommodated in Schedule 5 if the Committee were to impose a limit on pack size so as to limit the dose in the event of an accidental poisoning.

The Committee was of the view that the APVMA should ensure that adequate labelling to warn against application to cats or the danger of close contact between cats with treated dogs is imposed as part of the registration process.

## **DECISION 2004/42 – 6**

The Committee agreed to amend the Schedule 5 entry for permethrin to include preparations containing 50% per cent of less of permethrin when packed in single use containers having a capacity of 4 mL or less. Based on the toxicological data submitted by the sponsor, the Committee was satisfied that capping the product container size to 4 mL was appropriate for inclusion in Schedule 5.

## **SCHEDULE 5 – Amendment**

PERMETHRIN – Amend entry to read:

**PERMETHRIN:**

- (a) in preparations containing 25 per cent or less of permethrin;
- (b) in preparations for external use for the treatment of dogs containing 50 per cent or less permethrin when packed in single use containers having a capacity of 4 mL or less;

**except** in preparations containing 2 per cent or less of permethrin.

**4.7 SODIUM HYPOCHLORITE**

**PURPOSE**

The Committee considered the scheduling of sodium hypochlorite.

**BACKGROUND**

The scheduling of sodium hypochlorite was considered by the Committee as part of a class review of chlorinating compounds at the November 1999, February 2000, May 2000, November 2000, February 2002, June 2002 and October 2002 meetings. The Committee agreed to include an entry for chlorinating compounds in Schedule 6 with a cut-off to Schedule 5 at 20% available chlorine. During these considerations the Committee noted that sodium hypochlorite exhibited a low acute oral toxicity (LD50 of 8910 mg/kg bw) and agreed to exempt it from the requirements of scheduling. These amendments were included in SUSDP 18 Amendment 1 and came into effect on 1 September 2003.

At the June 2004 meeting, the Committee considered correspondence from Industry (XXXXXXXXXX) seeking clarification of the scheduling status of sodium hypochlorite solutions containing a low concentrations of sodium hydroxide. The company highlighted that sodium hypochlorite is manufactured via a reaction between sodium hydroxide and chlorine gas in water. In order to ensure that the equilibrium reaction is maintained in favour of hypochlorite formation and to prevent the liberation of chlorine gas, a small excess of sodium hydroxide is added to maintain the pH between 11 and 13. Consequently, commercially available preparations of sodium hypochlorite contain small quantities of sodium hydroxide ( $\leq 1\%$  w/v).

The Committee noted that currently sodium hypochlorite is currently exempt from the requirements of scheduling. However, the presence of sodium hydroxide would require these preparations to be labelled as either Schedule 5 or Schedule 6 poisons depending of the percentage of available chlorine and the pH of the particular solution.

Members were informed that the company had sought clarification of this issue from Queensland Health and was advised that “If a solution of sodium hypochlorite contains sodium hydroxide and the pH is above 11.5, it would still be scheduled based on its

alkalinity”. XXXXXXXXXX proposed that sodium hypochlorite solutions with a pH of less than 11.5 be exempt from the requirements of scheduling while those with a pH above 11.5 should remain scheduled. Furthermore, the Committee should ensure that the entry in the SUSDP preclude the intentional adjustment of strong chlorine solutions by the addition of sodium hydroxide. The Committee noted that by setting a sodium hydroxide cut-off at 1% w/v, the possibility of the intentional adjustment would be avoided. Furthermore, allowing for the presence of sodium hydroxide at this level would mirror the levels currently available in commercial preparations.

The Committee was of the view that, as the presence of a small amount of sodium hydroxide in sodium hypochlorite solutions is unavoidable, an exemption for such solutions was a reasonable proposition. Consequently, the Committee agreed to foreshadow the decision to exempt from the requirements of scheduling all sodium hypochlorite solutions containing not more than 1% sodium hydroxide and with a pH of less than 11.5.

## **DISCUSSION**

The Committee was informed that a public submission had been received from XXXXXXXXXX. XXXXXXXXXX advised that it noted the background and proposal with regard to sodium hypochlorite and supported the foreshadowed decision contained in the Record of Reasons for the June 2004 meeting.

A member advised the Committee that sodium hypochlorite solutions containing 1% sodium hydroxide would have a pH of approximately 12. Consequently, members were of the opinion that the phrase “containing not more than 1% sodium hydroxide” was unnecessary and thus agreed to remove it from the scheduling proposal foreshadowed at the June 2004 meeting.

Additionally, it was highlighted that preparations containing 5 per cent or less of sodium hydroxide with a pH of 11.5 or less were currently exempt from the SUSDP labelling requirements.

The Committee confirmed its view that sodium hypochlorite preparations containing a small amount of sodium hydroxide were exempt from the requirements of scheduling provided their pH was below 11.5. Members were of the view that the schedule entries for chlorinating compounds should also be amended so as to clarify that such preparation were exempt and to maintain consistency with other entries for substances exhibiting similar alkalinity.

## **DECISION 2004/42 – 7**

The Committee agreed to exempt from the requirements of scheduling all sodium hypochlorite preparations with a pH of less than 11.5.

### **Schedule 5 - Amendment**

CHLORINATING COMPOUNDS – Amend to read:

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

- (a) when separately specified in these Schedules;
- (b) sodium hypochlorite preparations with a pH of less than 11.5;
- (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.

### **Schedule 6 - Amendment**

CHLORINATING COMPOUNDS – Amend to read:

CHLORINATING COMPOUNDS **except:**

- (a) when included in Schedule 5;
- (b) when separately specified in these Schedules;
- (c) sodium hypochlorite preparations with a pH of less than 11.5;
- (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.

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

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

**6.1 IMINOCTADINE TRIALBESILATE**

**PURPOSE**

The Committee considered the scheduling of iminoctadine trialbesilate.

**BACKGROUND**

XXXXXXXXXX sought approval for the new active constituent iminoctadine trialbesilate and registration of the product XXXXXXXXXXXX, a suspension concentrate containing 300 g/L iminoctadine trialbesilate.

XXXXXXXXXX is proposed for use to control blossom blight (*Monilinia fructicola* and *M. laxa*) and brown rot (*M. fructicola*) on stone fruit (peach, nectarine, cherry, plum and apricot). The product proposed for registration, is formulated in Japan and will be imported into Australia fully labelled ready for distribution to warehouses and subsequent sale. It will be packaged in 0.5, 1, 5 and 20 L polyethylene containers. No home garden uses are proposed with the product to only be applied by farmers. XXXXXXXXXXXX or similar formulations are currently registered for use on various crops, including fruit and vegetables, in Asia (including Korea, China and Japan), the Middle East, Africa, Europe (Hungary, Turkey, Bulgaria) and Central America.



## **DISCUSSION**

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

[paragraphs removed]

Based on its acute oral and inhalational toxicity, the OCS recommended that an entry for iminoctadine trialbesilate be included in Schedule 6 of the SUSDP with a cut-off to Schedule 5 for preparations containing 30% or less of the substance.

The Committee was informed that the scheduling consideration of iminoctadine trialbesilate was included in the pre-October 2004 meeting gazette notice and no public submissions were received.

An expert member advised the Committee that an entry in Schedule 6 entry for iminoctadine trialbesilate was warranted given its toxicity profile. However, on the basis of the reproductive toxicity exhibited by the substance, a cut-off to Schedule 5 was inappropriate. Another member highlighted that the product containing the new active identified as a male reproductive toxin would be applied predominantly by young men several times during the growing season and that consequently, a Schedule 6 entry was appropriate. A member reminded that Committee that applicators would be required to wear protective equipment while using the product which would reduce exposure to the iminoctadine trialbesilate.

A member drew to the Committee's attention the product formulation details presented by the sponsor had identified the presence of XXXXXXXXXX, a class of potent sensitisers. The Committee noted the concerns expressed but reminded the member that the NDPSC was responsible for scheduling the active substances and not product formulations. Accordingly, the Committee agreed to advise that APVMA of the concerns expressed by the member.

## **DECISION 2004/42 – 8**

The Committee agreed to include an entry for iminoctadine trialbesilate in Schedule 6 on the basis of its toxicity profile.

### **Schedule 6 – New entry**

IMINOCTADINE TRIALBESILATE.

## **6.2 N-CYCLOHEXYLDIAZENIUMDIOXY-POTASSIUM**

### **PURPOSE**

The Committee considered the scheduling of N-cyclohexyldiazeniumdioxy-potassium.

### **BACKGROUND**

XXXXXXXXXX sought approval of the active constituent N-cyclohexyldiazeniumdioxy-potassium (K-HDO) and registration of XXXXXXXXXX, a liquid containing 275 g/L of K-HDO. K-HDO is a fungicide active against wood-destroying fungi (basidiomycetes). XXXXXXXXXX is a liquid preservative to be used to control this fungi in wood-based panels. It is mixed into the adhesive used for the manufacture of these products.

### **DISCUSSION**

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

[paragraphs removed]

Based on its acute oral toxicity, the OCS recommended that an entry for K-HDO be included in Schedule 6 of the SUSDP. A cut-off to a lower schedule was not supported due to the acute oral toxicity of the product.

The Committee was informed that the scheduling consideration of K-HDO was included in the pre-October 2004 meeting gazette notice and no public submissions were received.

An expert member advised the Committee that, on the basis of the toxicity profile, a Schedule 6 entry for K-HDO was warranted and there was no foundation for a cut-off to Schedule 5.

A member expressed concern at the possibility that K-HDO may leach out of the wood products into which it will be incorporated and that this may result in increased exposure, particularly to children. Another member advised the Committee that active substance is a salt that is unlikely to be volatile once incorporated into the wood adhesive and posed little risk. The evaluator also reminded the Committee that the substance was present in the finished wood products at very low levels.

### **DECISION 2004/42 – 9**

The Committee agreed to include an entry for K-HDO in schedule 6 of the SUSDP on the basis of its toxicity profile.

## **Schedule 6 – New entry**

N-CYCLOHEXYLDIAZENIUMDIOXY-POTASSIUM.

### **6.3 DELTAMETHRIN**

#### **PURPOSE**

The Committee considered the cut-off for deltamethrin to Schedule 5.

#### **BACKGROUND**

XXXXXXXXXX sought a change the poisons scheduling for the product XXXXXXXXXXXX, containing 250 g/kg deltamethrin as water dispersible granules, from Schedule 6 to Schedule 5. The company submitted argument to support this change, based on the re-packaging of the product and comparison with a current Schedule 5 product (XXXXXXXXXX). XXXXXXXXXXXX is for use on insect pests in domestic, commercial, industrial and public buildings, and associated external areas.

An entry for deltamethrin was initially included in Schedule 6 of the SUSDP at the February 1979 meeting. Following consideration at the May 1979 meeting the entry for deltamethrin was moved to Schedule 7 due to occupational health concerns. The Schedule 7 classification of deltamethrin was reviewed several times in the following years and ultimately confirmed in November 1988 based on the available acute and chronic toxicity data. Also at the November 1988 meeting and as a consequence of the scheduling consideration of XXXXXXXXXXXX, an aqueous suspension formulation of 1 per cent deltamethrin, in no organic solvent other than a glycol, an entry for deltamethrin was included in Schedule 5. XXXXXXXXXXXX, containing 2.5 per cent of deltamethrin was included in Schedule 6 in February 1993. Over the years, a wide range of products containing deltamethrin were considered by the Committee for inclusion in Schedule 5 or Schedule 6.

The scheduling of deltamethrin when included in XXXXXXXXXXXX was considered by the Committee at the February 2002 meeting. The Committee agreed that, although the acute toxicity profile of the product was appropriate for Schedule 5, members remained concerned of the potential for neurotoxicity and the likely flow-on effects for other deltamethrin products. Accordingly, the Committee agreed that the product should be labelled as a Schedule 6 poison.

#### **DISCUSSION**

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

[paragraphs removed]

On consideration of these issues, the OCS recommended that the Committee consider amending the Schedule 5 entry for deltamethrin to include XXXXXXXXXX packaged in unit dose child-resistant sachets.

Members were informed that a public submission was received from XXXXXXXXXX which advised that it has an interest in deltamethrin and sought the right to make a post-meeting comment.

In accordance with new arrangements, members noted that the OCS evaluator requested that the sponsor provide a sample of the product packaging for the Committee's consideration. The sponsor advises that a sample of the packaging was unlikely to be available for consideration at the October 2004 meeting. The Committee noted that the sponsor had not provided any evidence to support the claim that the proposed product packaging was child-resistant. However, the sponsor has indicated that the packaging would comply with Section 3 of AS1928-2001 Requirements for Child Resistant Packaging-Non Reclosable. Photographs of the proposed packaging were provided for consideration.

A number of members expressed concern that the sponsor was unable to provide a sample of the product packaging and that the provision of photographs as a substitute was of little assistance in assessing the child-resistance potential of the packaging.

The XXXXXXXXXX Member reminded the Committee that sponsors had been asked to provide product samples in the event that the proposed packaging did not comply with a recognised standard. In this case, the sponsor had advised the packaging would comply with AS1928-2001.

A member expressed the opinion that insuring that claims of compliance with a particular standard are an issue for the relevant registration authority and that the Committee need only be satisfied that employing such a measure would effect the desired health and safety outcome. Given sponsor's proposal and the OCS recommendation, should the Committee consider it appropriate, a member suggested that the APVMA be advised that they should ensure that the packaging is compliant with AS1928-2001 prior to the product being marketed.

#### **DECISION 2004/42 – 10**

The Committee agreed to amend the Schedule 5 entry for deltamethrin in accordance with the sponsor's request. The Committee further agreed that the APVMA be advised that they should ensure that the packaging is compliant with AS1928-2001 prior to the product being marketed

#### **Schedule 5 – Amendment**

DELTAMETHRIN – Amend entry to read:

DELTAMETHRIN:

- (a) in aqueous preparations containing 1 per cent or less of deltamethrin, when no organic solvent, other than a glycol, is present;
- (b) in wettable granular preparations containing 25 per cent or less of deltamethrin when packed in child-resistant packaging each containing 3 grams or less of the formulation;
- (c) in water-dispersible tablets each containing 500 mg or less of deltamethrin in child-resistant packaging; or
- (d) in other preparations containing 0.5 per cent or less of deltamethrin.

**6.4 PINE OILS**

**PURPOSE**

The Committee considered a Schedule 5 cut-off for pine oils.

**BACKGROUND**

The scheduling of pine oils was considered at the February 2004 meeting at which XXXXXXXXXX sought an extension of use for their home garden product, XXXXXXXXXX containing 680 g/L pine oil) to allow commercial broadacre use. Pine oils are refined from the  $\alpha$ -pinene fraction of the crude sulfate turpentine extract of *Pinus radiata*. Once applied to target plants, XXXXXXXXXX removes the waxes from the outer skin of the foliage and promotes dehydration and plant death.

Historically, both pine oils and pinene has been exempt from scheduling requirements through inclusion in Appendix B. Although there was some literature about the intoxication of humans with pine oil derivatives, these substances have had widespread use over a long time and in the past the Committee had not considered there to be a significant problem. However, these entries were removed from Appendix B at the May 1985 meeting due to no data indicate safety in human use being received by the Committee during its review of essential oils.

The Committee noted that the OCS evaluation report identified the product, XXXXXXXXXX, as a moderate skin irritant and a severe eye irritant and that it would appear to be unsuitable for home garden use. Consequently, the Committee agreed to include pine oils derived from *Pinus radiata* in Schedule 6 when packaged and labelled for use as a herbicide on the basis that it is a moderate skin irritant and a severe eye irritant. The entry for pine oils was included in SUSDP 19 Amendment No 1, effective 1 September 2004.

XXXXXXXXXX submitted new studies on eye irritancy and dermal toxicity in rabbits for the concentrated product (68%) and two ready-to-use premixes (10% and 20%). The sponsor sought a reconsideration of the scheduling of pine oil with a view to the Committee setting a cut-off to Schedule 5.

## **DISCUSSION**

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

[paragraphs removed]

On the basis of the data presented, the OCS recommended the inclusion of pine oils at 20% or less in Schedule 5 of the SUSDP.

The Committee was informed that XXXXXXXXXXXX submitted public comment in which the company advised that they have an interest in pine oil and wish to reserve the right to make a post meeting comment. XXXXXXXXXXXX further advised that the company uses pine oils as perfumes at a level of 0.002% and that these were derived from *Pinus radiata*.

A number of members expressed the opinion that the irritancy profile exhibited by the 20% preparation of pine oils warranted scheduling and that an entry in Schedule 5 was appropriate.

In light of the comments received from industry, the Committee was of the opinion that limiting the schedule entries for pine oils to a specific use may be inappropriate on the basis of its acute oral toxicity and widespread use in consumer products. Accordingly, members proposed that the Secretariat investigate this matter further and report to the February 2005 meeting.

## **DECISION 2004/42 – 11**

The Committee agreed to include pine oils at 20 per cent or less in Schedule 5 when packaged and labelled for use as a herbicide.

### **Schedule 6 – Amendment**

PINE OILS – Amend entry to read:

PINE OILS (derived from *Pinus radiata*) when packed and labelled for use as a herbicide **except** when included in Schedule 5.

## **Schedule 5 – New entry**

PINE OILS (derived from *Pinus radiata*) in preparations containing 20 per cent or less pine oils when packed and labelled for use as a herbicide.

### **6.5 PYRITHIONE COPPER**

#### **PURPOSE**

The Committee considered the scheduling of pyrrithione copper.

#### **BACKGROUND**

XXXXXXXXXX sought approval for a new active constituent, pyrrithione copper. Pyrrithione copper is a member of the cyclic thiohydroxamic acids and is proposed for use in anti-fouling paints on marine surface vessels. The powder is manufactured in Ireland and packed in anti-static bags, which are then placed in steel drums for export to Australia.

#### **DISCUSSION**

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

[paragraphs removed]

Based on its acute toxicological profile, in particular its acute inhalation toxicity and severe eye irritancy/corrosivity, the OCS recommended that an entry for pyrrithione copper be included in Schedule 6 of the SUSDP.

Members noted that there were no products listed on the ARTG or PUBCRIS databases containing pyrrithione copper.

Members were informed that the scheduling consideration of pyrrithione copper was included in the October 2004 pre-meeting gazette notice and no public submission was received.

An expert member expressed the opinion that given the substances intended use and toxicity profile an entry in Schedule 6 was appropriate.

Another member highlighted that pyrrithione copper is corrosive to the eye and expressed the view that perhaps an entry in Schedule 7 was more appropriate. The member was advised that this issue had been raised at the time pyrrithione zinc was considered by the Committee and subsequently included in Schedule 6. The Committee opted for a less restrictive schedule in order to make anti-fouling paints containing pyrrithione zinc available to recreational boat owners and was justified on the grounds that appropriate

label warnings and personal protective equipment (PPE) would reduce the risk to users. The XXXXXXXXXX Member advised the Committee that the OCS would also be making occupational health and safety recommendations in relation to this active, including recommendations regarding PPE. Accordingly, members agreed that the APVMA should be made aware of the Committee's concerns and that appropriate steps be taken through labelling by the regulatory authority to safeguard against eye injury.

## **DECISION 2004/42 – 12**

The Committee agreed to include pyrethrin copper in Schedule 6 on the basis of its acute toxicological profile.

### **Schedule 6 – New entry**

PYRETHRIN COPPER.

## **6.6 PYRAFLUFEN ETHYL**

### **PURPOSE**

The Committee considered the scheduling of pyraflufen-ethyl.

### **BACKGROUND**

XXXXXXXXXX sought approval for a new active ingredient, pyraflufen-ethyl. The new active will in due course be incorporated into a new herbicide product for use to control post-emergent broadleaf weeds in crops such as cotton, wheat and barley.

Pyraflufen-ethyl belongs to the phenyl pyrazole class of chemicals called protoporphyrinogen inhibitors (protox inhibitors). Pyraflufen-ethyl is a novel inhibitor of protoporphyrinogen IX oxidase. The inhibition of this enzyme in chloroplasts causes the accumulation of protoporphyrinogen IX, which results in peroxidation of foliar cell membrane lipid under the presence of light, with subsequent cell membrane destruction and necrosis.

### **DISCUSSION**

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

[paragraphs removed]

Based on its low toxicological hazard, the OCS recommended that pyraflufen-ethyl be exempt from the requirements of scheduling.



The Committee was informed that the scheduling consideration of pyraflufen-ethyl was included in the October 2004 pre-meeting gazette notice and no public submission were received.

An expert member expressed concern that because pyraflufen-ethyl belongs to a class of chemicals that inhibits protoporphyrinogen oxidase it could have a profound effect on people susceptible to porphyria. Accordingly, it was proposed that an exemption from the requirements of scheduling for pyraflufen-ethyl would be inappropriate. A member drew to the Committee's attention to the OCS evaluation report which identified pyraflufen-ethyl as having toxic effects on erythrocytes resulting in anaemia.

Members expressed concern that the data presented was deficient in information regarding pyraflufen-ethyl's potential to precipitate an attack of porphyria including risk reduction measures such as label warning statements used on products marketed overseas.

It was the view of the members that there was insufficient information before the Committee for a scheduling decision to be made.

## **OUTCOME**

The Committee agreed to defer consideration of the scheduling of pyraflufen-ethyl in order to seek more information regarding porphyrin metabolism, including measurements of relevant parameters and comment on the product's potential to trigger an attack of porphyria.

### **6.7 CYHALOFOP BUTYL**

#### **PURPOSE**

The Committee considered the scheduling of cyhalofop-butyl.

#### **BACKGROUND**

XXXXXXXXXX sought approval for a new active constituent, cyhalofop-butyl, and the registration of a new product XXXXXXXXXXXX containing 285 g/kg cyhalofop-butyl.

Cyhalofop-butyl is a member of the aryloxyphenoxy propionate group of herbicides. Its herbicidal activity is mediated via the inhibition of acetyl coenzyme-A carboxylase, a pivotal enzyme involved in plant fatty acid synthesis. The product, XXXXXXXXXXXX is intended for the post-emergence control of barnyard grasses and silver top in rice. It will be marketed in Foam High Density Polyethylene (FHDPE) containers as 5, 10 and 20 L packs.

## **DISCUSSION**

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

[paragraphs removed]

Consequently, the OCS recommended that an entry for cyhalofop-butyl be included in Schedule 5 of the SUSDP.

The Committee was informed that the scheduling consideration of cyhalofop-butyl was included in the October 2004 pre-meeting gazette notice and no public submission were received.

A member expressed the opinion that despite its low acute oral, dermal and inhalational toxicity an entry for cyhalofop-butyl in Schedule 5 was warranted on the grounds of its toxicity to the liver and kidneys.

Members noted that the proposed formulation had been identified as a severe eye irritant. The Committee was of the view that the OCS and the APVMA should ensure that the first aid instructions and safety directions applied to the product are sufficient to protect users of the product against eye damage.

## **DECISION 2004/42 – 13**

The Committee agreed to include an entry for cyhalofop-butyl in Schedule 5 on the basis of its liver and kidney toxicity.

### **Schedule 5 – New entry**

CYHALOFOP-BUTYL.

## **6.8 PROCYMIDONE**

### **PURPOSE**

The Committee considered the scheduling of procymidone.

### **BACKGROUND**

The February 2004 meeting the Committee considered the scheduling of procymidone in relation to an extension of use application for XXXXXXXXXX and XXXXXXXXXX. Both products are suspension concentrate (SC) formulations containing 500 g/L procymidone as the active constituent. The Committee noted the Office of Chemical Safety (OCS) evaluation report which identified procymidone as a reproductive and developmental toxin in laboratory animals and recommended that an entry in Schedule 7 for the substance was appropriate. Accordingly, the Committee agreed to include an entry for

procymidone in Schedule 7 on the basis of its teratogenic potential. The Schedule 7 entry was included in SUSDP 19 Amendment 1 which came into effect on 1 September 2004.

In response to the evaluation report, XXXXXXXXXX advised that additional toxicity data addressing the concerns raised regarding procymidone were available and requested that this information be presented to the Committee for their consideration. The Committee noted with some concern that additional toxicological data for procymidone was only made available after the applicant was advised of the recommendations in the OCS evaluation report.

The OCS presented an evaluation report reviewing the additional toxicological studies submitted by XXXXXXXXXX for the Committee's consideration.

The OCS evaluation report also included a review of comments made by the sponsor in response to the initial OCS evaluation for procymidone.

## **DISCUSSION**

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

[paragraphs removed]

After consideration of the data presented by the sponsor, the OCS initially recommended the scheduling of procymidone remained appropriate. However, based on the new data submitted, the OCS recommended the entry in Schedule 7 be deleted and an entry for procymidone be included in Schedule 6 of the SUSDP.

Members expressed concern that, despite the new data submitted by the sponsor, there was evidence that procymidone promoted anti-androgenic effects in-vitro in human cell lines. Therefore despite the absence of effects in the monkey studies submitted, the possibility of endocrine disrupting effects in human could not be discounted.

## **OUTCOME**

Notwithstanding the additional data submitted by the company, the Committee was of the view that concern was warranted in light of the in-vitro human cell line data. Accordingly, the Committee considered the current scheduling of procymidone remained appropriate.

## **6.9 BUTORPHANOL**

### **PURPOSE**

The Committee considered a proposal to down-schedule butorphanol from Schedule 8 to Schedule 4.

## BACKGROUND

The Committee considered the scheduling of butorphanol at its November 1986 meeting. The Committee agreed with the evaluator and recommended that entries for butorphanol be included in Schedule 8 and Appendix D on the basis of its potential for abuse. At the time the Committee was aware that butorphanol was classified as a prescription medicine overseas and was not of apparent concern to the WHO as a potential drug of addiction.

At the August 1995 meeting, the Committee considered a proposal to down-schedule butorphanol from Schedule 8 to Schedule 4. The sponsor argued as butorphanol for human therapeutic use was in the equivalent to Schedule 4 in most countries, a similar scheduling characterisation should be adopted in Australia. The Committee noted with concern reports from the USA of an increasing trend towards human abuse and misuse patterns, including the beginnings of illicit trafficking. One form of butorphanol, a nasal spray formulation had demonstrated a substantial potential for abuse since its introduction in the US in 1992. The Committee was of the view that with increased availability, the risk of abuse could only increase. Furthermore, in the absence of a supporting submission from veterinary practitioners requesting easier access, rescheduling could not be supported and agreed that an entry in Schedule 8 for butorphanol remained appropriate.

XXXXXXXXXX sought rescheduling of butorphanol from Schedule 8 to Schedule 4 of the SUSDP. Butorphanol is synthetic, centrally acting, opioid agonist – antagonist analgesic with potent antitussive activity. It is a member of the phenanthrene class of compounds and is related structurally to morphine, but exhibits pharmacological activity similar to other partial agonists such as pentazocine and nalbuphene.

The product is administered by IM, SC or IV injection to dogs and cats at a dose of 0.01 – 0.03 or 0.01 – 0.04 mL/kg bw, respectively, equivalent to 0.1 – 0.3 and 0.1 – 0.4 mg butorphanol/kg bw. Horses are treated by IV injection at 0.2 – 1.0 mL/100 kg bw, delivering a maximum recommended dose of 0.1 mg butorphanol/kg bw. Butorphanol may be combined with a sedative such as xylazine, detomidine or romifidine to “chemically restrain” horses in a standing position. This allows procedures including diagnostic examination and imaging, dentistry, minor surgery and castration to be performed without general anaesthesia, which has a higher risk to horses compared with most other species.

Butorphanol (as butorphanol tartrate) is the active constituent in three veterinary medicine products that are registered in Australia. All such products contain butorphanol tartrate at 10 mg/mL, and are used as an analgesic and sedative in horses, dogs and cats. Butorphanol is not used as a human medicine in Australia. However, there are currently two injectable products listed on the ARTG containing butorphanol (as butorphanol tartrate) for human use but both are intended for export only. There are currently no human therapeutic products containing butorphanol in New Zealand.

## DISCUSSION

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

- The NDPSC has considered butorphanol on two previous occasions. In November 1986, the committee placed butorphanol in Schedule 8 with an Appendix D rider stipulating that the substance should be available for use in horses only. (This Appendix D restriction is no longer current.) Although the Committee was aware that butorphanol was in Schedule 4 in overseas jurisdictions, Schedule 8 was considered appropriate due to the potential for abuse.
- The NDPSC considered a submission to reschedule butorphanol from Schedule 8 to Schedule 4 at its August 1995 meeting. The committee noted that butorphanol was used in Australia for veterinary purposes only, and that a WHO (1989) review had concluded that butorphanol did not need to be placed under international control because it caused few public health and social problems. However, the NDPSC was concerned that other veterinary drugs such as anabolic steroids had become drugs of human abuse when access was not restricted, and that abuse of race horses with narcotic analgesics could cause serious injury or death to both horse and rider. The NDPSC also observed that there was no demonstrated support for the proposal from veterinary practitioners, and that the USA was considering controls to limit access and availability of butorphanol because of illicit use. Based on these considerations, rescheduling was not supported.
- In the current submission, XXXXXXXXXX have advanced several arguments for rescheduling butorphanol from Schedule 8 to Schedule 4. Firstly, butorphanol is not included in Schedule I or II of the WHO Single Convention on Narcotic medicines, or in Schedule II or III of the WHO Convention on Psychotropic Substances, having been considered to pose only “low to moderate” potential for abuse by the WHO Expert Committee on Drug Dependence (1989). Second, butorphanol is available as a prescription medicine or prescription veterinary medicine in many countries (including the UK, New Zealand and Canada). Following the introduction into the US market of a nasal spray for human use, butorphanol has been classified as a Schedule IV drug by the US Drug Enforcement Agency. Furthermore, the applicant contends that butorphanol does not meet the NDPSC’s criteria for classification in Schedule 8, and that the rescheduling of butorphanol into Schedule 4 would be in keeping with Trans-Tasman harmonisation of medicines scheduling. XXXXXXXXXX also suggest that the Schedule 8 status of butorphanol is restricting its use in equine medicine, where the drug is said to offer animal welfare and occupational health and safety advantages. The applicant describes the record-keeping and storage requirements for Schedule 8 drugs as “inconvenient to veterinarians”, and states that veterinarians have concerns as to their legal responsibilities and security of Schedule 8 drugs when kept in vehicles during their rounds. The submission includes a letter from XXXXXXXXXX the proposed rescheduling.

- From a toxicological viewpoint, consideration could be given to the proposal to place butorphanol in Schedule 4. Butorphanol is of moderate acute oral toxicity in rodents and is currently registered as 10 mg/mL injectable solutions for veterinary use in a limited range of companion animal species. Under current circumstances, public exposure to the drug within Australia is probably negligible.
- The limited information available indicates that butorphanol is not genotoxic, carcinogenic or teratogenic, although it may cause foetotoxicity in laboratory species at oral doses of 30 mg/kg bw and greater.
- Butorphanol tartrate is used as a human medicine in some overseas jurisdictions, including the USA.
- Butorphanol neither precipitates nor suppresses a withdrawal syndrome in morphine-dependent patients, but does precipitate a withdrawal syndrome in methadone-dependent individuals. After long-term administration of butorphanol, the abrupt withdrawal of the drug or administration of naloxone produces a withdrawal syndrome similar to that which follows use of cyclazocine (Reisine & Pasternak, 1996). According to these authors, few cases of butorphanol abuse have been reported since the drug was introduced in 1978.
- However, the Physicians' Desk Reference (1996) states that among 161 patients who used butorphanol nasal spray for two months or longer, approximately 3% had behavioural symptoms suggestive of possible abuse. Approximately 1% of these patients reported significant overuse. Furthermore, the US Drug Enforcement Agency considers butorphanol to be a "drug of abuse" (see <http://www.usdoj.gov/dea/concern/butorphanolp.html>) and Jordan & Catterton (2003) have described use of butorphanol by injection as a recreational drug (see <http://www.usdoj.gov/dea/programs/forensicsci/microgram/mg0103/mg0103.html>).
- Notwithstanding its previous (1989) recommendation against international control, the WHO Expert Committee on Drug Dependence (2003) has now recommended the critical review of butorphanol, based on a significant number of reports of abuse, withdrawal syndrome and dependence originating mainly from Canada, Italy, the UK and USA. The committee noted that butorphanol "ranks first in the list of all drugs for which drug dependence has been reported as an adverse drug reaction to the WHO International Drug Monitoring Programme".
- Although control of use issues lie beyond the toxicological domain, the NDPSC may wish to consider the implications of the above information for the proposed revision of the Schedule 8 Poisons Schedule status of butorphanol.

The OCS advised that on the basis of toxicity, there appears to be justification to include butorphanol in Schedule 4 of the SUSDP. However, in light of a significant number of reports of abuse, withdrawal syndrome and dependence originating mainly from Canada, Italy, the UK and USA, the OCS recommended that the Schedule 8 entry for butorphanol in the SUSDP be retained.

The Committee was informed the public submissions mostly supporting the rescheduling proposal were received from the XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX. The Committee noted that the many of these submissions appeared to be in response to a letter sent to veterinarians by XXXXXXXXXX.

The consensus of opinion amongst the veterinarians who made submissions to the NDPSC was overwhelmingly in support of the proposal to down-schedule butorphanol to Schedule 4. The down-scheduling was supported on the grounds that an entry for butorphanol in Schedule 4 would:

- Harmonise the scheduling of butorphanol in Australia with other countries throughout the world such as NZ and USA;
- Reduce the regulatory burden on veterinarians with regards to storage and transportation of the substance and, consequently, reduce the cost to clients; and
- Encourage greater use of chemical restraint methods which improve occupational health and safety of personnel and the pain management of the animal being treated.

Furthermore, the abuse of veterinary injectable preparations of butorphanol has not been reported.

The Committee noted that XXXXXXXXXX from the XXXXXXXXXX opposed the proposal to down-schedule butorphanol on the basis that it is a potentially dangerous drug when misused and was open to abuse. Furthermore, he considered that the equine industry, especially the equine stud industry, has a remarkably cavalier attitude to drugs on studs being used by non-veterinarians such as grooms and horse handlers.

In a second submission from the sponsor, members noted the argument that the down scheduling of butorphanol to Schedule 4 would also reduce the off-label use of substances such as buprenorphine and methadone in veterinary practice.

The Committee noted that the OCS Treaties and Monitoring Section submitted the following points for consideration:

- The importation of butorphanol was brought under the control of Regulation 5 of the Customs (Prohibited Imports) Regulations 1956 in 1999. At the same time, the export of butorphanol was brought under the control of Regulations 10 - 10F of the Customs (Prohibited Exports) Regulations 1958. The then Minister for Health and Aged Care, the Hon Dr Michael Wooldridge MP cited public health concerns over designer drugs as the reasoning for inclusion of this substance in these regulations. Butorphanol is not included in any of the three United Nations drug treaties to which Australia is a signatory.
- Butorphanol is currently entered as Item 32A in Schedule 4 of the Customs (Prohibited Imports) Regulations and as Item 4A of Part 3 of Schedule 8 of the

Customs (Prohibited Exports) Regulations. This requires that a prospective importer or exporter of butorphanol must hold a Licence to Import or a Licence to Export under the relevant Regulation and must also be issued a permit to import or a Permit to Export for each shipment.

- Licences and permits to import or export are issued by the OCS.
- As a consequence of butorphanol being included in Schedule 8 of the SUSDP, and in accord with Regulation 5(9)(g) of the Customs (Prohibited Imports) Regulations all manufacture of preparations containing butorphanol and domestic movements between State licensed entities must be reported to the OCS on a weekly basis.

Members noted that there appeared to be evidence of butorphanol abuse in several countries which had recently prompted the WHO Expert Committee on Drug Dependence to recommend a critical review of the substance. Whilst the Committee recognised that the entry in Schedule 8 for butorphanol imposed addition storage and security requirements on veterinarians, members were of the view that it was inappropriate at this time to change the scheduling of the substance prior to the outcome of the WHO review.

## **OUTCOME**

The Committee agreed that the current scheduling of butorphanol remained appropriate.

### **6.10-6.11 POTASSIUM SORBATE/SODIUM PROPIONATE**

## **PURPOSE**

The Committee considered the scheduling of potassium sorbate and sodium propionate.

## **BACKGROUND**

XXXXXXXXXX sought the registration of a new product called XXXXXXXXXXXX which is an emulsion formulation containing four active constituents, lanolin, benzalkonium chloride, potassium sorbate and sodium propionate at a concentration of 83, 12, 2 and 2 g/L, respectively. The product is proposed for use as a timber preservative against wood rot fungi, termites, mould, and physical damage. It is also a timber treatment product.

Lanolin is usually used as a non-active constituent in many registered products, and is currently on the APVMA active constituent exempt list. Benzalkonium chloride is also known as N-alkyl dimethyl benzyl ammonium chloride, and is currently on the APVMA active constituent exempt list. Benzalkonium chloride is included in Schedule 6 of the SUSDP for concentrations greater than 10%, and in Schedule 5 for concentrations between 5 and 10%. An ADI for benzalkonium chloride has not been established because of insufficient data available to enable this.



Potassium sorbate is a common mouldicide used for food products such as bread and cheese. Currently, potassium sorbate is not approved by APVMA as an active constituent. Sodium propionate is the sodium salt of propionic acid, a simple three-carbon carboxylic acid. It is used as a fungicide and for mould prevention, and most uses are as a food additive in baked goods, confectionery and gelatin. It is also used in cosmetics and as a topical antifungal for livestock. The applicant claimed that sodium propionate is frequently used in conjunction with potassium sorbate. This chemical occurs naturally in various traditional cheeses and historically has been used as a preservative in biological fertilisers such as fish and kelp meal. Humans produce propionic acid and its salts as part of the normal metabolic process. Sodium propionate is toxic to moulds and certain bacteria at concentration of 0.02-0.05% due to the inability of the affected organism to metabolise the three-carbon chain. Its main antimicrobial effect is attributed to the undissociated acid penetrating the microbial cell wall and then disassociating in the higher pH cytoplasm. The  $H^+$  release is believed to inhibit glycolysis and growth. Sodium propionate is not approved as an active constituent.

## DISCUSSION

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

- Potassium sorbate has low acute oral toxicity (LD50 = 4340 mg/kg bw in rats). According to the MSDS provided by the applicant, potassium sorbate may be a slight skin and eye irritant, and will irritate the respiratory system if inhaled.
- Sodium propionate has low acute oral toxicity (LD50 = 5600 mg/kg in rats, or 5100 mg/kg bw in mice). In repeat dose toxicity studies in rats, the application of sodium propionate up to 2490 mg/kg bw/day did not reveal treatment-related changes in haematology, clinical chemistry, urinalysis and histopathology. Only slightly fore-stomach changes were observed at 3320 mg/kg bw/day in a 4-week rat study. In a 9-week monkey study, no overt toxic effects were observed at 420 mg/kg bw/day. Sodium propionate has no genotoxic effects in a range of genotoxicity studies.

Given that potassium sorbate and sodium propionate are food additives and have low toxicity profiles, the OCS recommended that both potassium sorbate and sodium propionate be exempt from the requirements of scheduling.

The Committee noted that public submissions were received from XXXXXXXXXX and XXXXXXXXXX.

- The XXXXXXXXXX advised that sorbic acid and potassium sorbate have been reviewed by the USA Cosmetic Ingredient Review Expert Panel and their findings have been published in JACT 7(6) 1988. They found sorbic acid and potassium sorbate to be safe as cosmetic ingredients in the present practices of use and concentration. The XXXXXXXXXX offered to provide a copy of this report prior to the October meeting if requested. Potassium sorbate and sorbic acid are used in cosmetics as preservatives and are typically used at levels of 0-1%.

- XXXXXXXXXX advised that they have an interest in potassium sorbate and sodium propionate and sought the right to make post-meeting comment.

**DECISION 2004/42 – 14**

The Committee agreed to exempt potassium sorbate and sodium propionate from the requirements of scheduling on the basis of low toxicity.

**Appendix B – New entries**

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
POTASSIUM SORBATE	October 2004	a	1.3
SODIUM PROPIONATE	October 2004	a	1.3

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

No items were considered.

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

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

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

The Commonwealth Government’s response to the JETACAR Report accepted “the concept that all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)”. However, the Government’s acceptance was qualified by highlighting that “... certain antibiotic products might be exempted from this scheduling class where the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA) and the NDPSC assess the antibiotic products as having a low and acceptable risk of promoting antibiotic resistance”. Additionally, it was the Government’s view that when implementing controls on in-feed and drinking water use of antibiotics for animals (including fish) full account should be taken of established industry codes that are implemented through third party audited quality assurance programs incorporating veterinary authorisation.

The Committee agreed at the June 2002 Meeting that the scheduling of antibiotics currently registered with the APVMA and listed outside of Schedule 4 in the SUSDP would be reviewed. This intention was included in the post - October 2002 meeting notice published in the Commonwealth of Australia Gazette No GN 49, 11 December 2002.

The Committee gazetted for consideration sulfacetamide, tetracycline, chlortetracycline and oxytetracycline at the October 2004 meeting. Sulfacetamide (8.1) was considered as an individual item while the tetracyclines (8.2-8.4 – tetracycline, chlortetracycline and oxytetracycline) were considered collectively. [sentence removed]

## **8.1 SULFACETAMIDE**

### **PURPOSE**

The Committee considered the scheduling of the sulfacetamide.

### **BACKGROUND**

At the June 2004 meeting, the Committee considered the scheduling of the sulfonamides, including sulfacetamide under JETACAR Recommendation 6. The Committee noted that a submission had been made by XXXXXXXXXX. The company advised that it marketed a human topical preparation, labelled as a Schedule 3 product, indicated for the treatment of minor ocular infections such as mild to moderate conjunctivitis containing 10% sulfacetamide.

The XXXXXXXXXX submission was assessed by EAGAR which recommended that sulfacetamide be rescheduled to Schedule 4 on the basis that the potential to develop resistance. During the deliberations a member expressed concern that there appeared to be no evidence to indicate that the EAGAR had taken the XXXXXXXXXX submission into account. The Committee also noted that a decision to reschedule sulfacetamide from Schedule 3 to Schedule 4 in accordance with the EAGAR recommendation would lead to an unharmonised scheduling position with New Zealand. The Committee sought confirmation from EAGAR that it considered the public submission from XXXXXXXXXX before recommending that all sulfonamides used in human and non-food producing animals be included in Schedule 4. EAGAR advised that the XXXXXXXXXX submission had been taken into consideration and that the Committee should note its initial recommendation regarding the scheduling of the sulfonamides. However, the Committee thought it appropriate that the XXXXXXXXXX submission be independently reviewed and advice obtained on whether maintaining an entry for a 10% sulfacetamide preparation in Schedule 3 presented an unacceptable risk of promoting antibiotic resistance. It was agreed that the scheduling of sulfacetamide would be further considered at the October 2004 meeting.

The Committee recommended the inclusion of all sulfonamides except those used on ornamental fish and caged ornamental birds in Schedule 4. This decision will be

published in SUSDP 19 Amendment 2 which is expected to come into effect on 1 January 2005.

Sulfonamides inhibit the growth of bacteria by interfering in the biosynthesis of folic acid, essential for the production of amino acids and nucleotides. Within the folic acid pathway, dihydropteroate synthase (DHPS) catalyses the synthesis of 7,8-dihydropteroate from pterin pyrophosphate and para-aminobenzoate (PABA); sulfonamides compete with PABA for this enzyme and inhibit its activity.

## DISCUSSION

The Committee was informed that XXXXXXXXXX had made another public submission. The company advised that it did not agree with the EAGAR recommendation and believes that ophthalmic sulfacetamide should remain a Schedule 3 product for the following reasons:

- The 10% ophthalmic solution is topically applied and acts locally with a very low rate of systemic absorption compared to other antibiotics of its class.
- The down-scheduling in 1996 to Schedule 3 was based on demonstrated safety, confidence in pharmacists ability to appropriately diagnose conjunctivitis and recommend the product, the Trans-Tasman harmonisation and support from significant stakeholders.
- Resistance to sulfonamides is not increasing and there is limited cross-resistance to other antibiotics.
- An entry in Schedule 3 allows for appropriate usage and reduces burden on Medicare.
- There are limited antibiotic alternatives for the treatment of ocular infections.
- The JETACAR report classified the sulfonamides as Category C substances, that is, those with a reasonable number of alternatives from other classes available. Therefore, the consequence of resistance to the sulfonamides would be minor compared to that of resistance of a Category A antibiotic.

In accordance with new arrangements (see item 8.5), an independent assessment of the XXXXXXXXXX submission was prepared by XXXXXXXXXX. The evaluation report raised the following points for consideration:

- Topical sulfonamides are not recommended standard therapy for any eye infections including mild to moderate conjunctivitis or other minor eye and adnexa infections by Australian experts. (Therapeutic Guidelines – Antibiotic, Version 12, 2003).
- Sulfonamides are broad spectrum agents that have the potential to select for multi-resistance in common bacterial pathogens harboured in the upper respiratory tract, including eye pathogens.
- Use of topical ophthalmic sulfacetamide has increased in Australia at the expense of Schedule 2 rather than Schedule 4 preparations.

- On the basis of the above information, the evaluator recommended that topical ophthalmic sulfacetamide be rescheduled to Schedule 4.

Members were informed that the independent assessment and the XXXXXXXXXX submission to the October 2004 meeting were forwarded to EAGAR for peer review and comment. EAGAR advised that, based on the recommendations in XXXXXXXXXX's evaluation, it would be in Australia's interest that topical ophthalmic sulfacetamide be rescheduled to Schedule 4. EAGAR also advised that XXXXXXXXXX abstained from commenting on the reviews provided by NDPSC.

The Committee was advised that public comment was received from XXXXXXXXXX. XXXXXXXXXX supported the inclusion of sulfacetamide in Schedule 4 because of the relentless and increasing emergence of antibiotic resistance.

A member expressed the opinion that there did not appear to be any significant evidence in the literature that the use of ophthalmic sulfacetamide had caused an increase in antibiotic resistance. Furthermore, studies in the United Kingdom had shown that the levels of resistance to the sulfonamide antibiotics over the past 30 years had remained essentially static despite their continued use.

Members also expressed the view that moving ophthalmic sulfacetamide to Schedule 4 would limit the availability of a valuable initial treatment for mild conjunctivitis and thus could promote the use of antibiotics that are of greater importance to public health.

## **OUTCOME**

The Committee agreed that the current scheduling of ophthalmic sulfacetamide remained appropriate. Continued Schedule 3 status was seen as providing an appropriate level of access under the supervision of a pharmacist.

### **8.2-8.4 TETRACYCLINES**

#### **PURPOSE**

The Committee considered the scheduling of the tetracyclines.

#### **BACKGROUND**

The February 1971 meeting included an entry in Schedule 6 allowing the use of tetracycline for veterinary purposes, for topical application for ocular use only, or when suitably coloured as a marker and when specifically packed in applicator devices designed for inter-mammary infusion in the treatment of animals. In 1981 the Committee amended the Schedule 6 entries for tetracycline, chlortetracycline and oxytetracycline to limit the dose in veterinary products to 100000 international units per dose and to include a colouring agent. At the February 1996 meeting, the Committee included an entry for 40% tetracycline preparations in Schedule 5 when packed and labelled for the treatment

of ornamental caged birds or ornamental fish. The August 1997 Meeting of the NDPSC considered the re-scheduling, from Schedule 6 to Schedule 5, of oxytetracycline preparations containing 40% or less of oxytetracycline when packed and labelled for the treatment of caged birds. As tetracycline was already included in Schedule 5 for this purpose, and for the treatment of ornamental fish, the Committee recommended that tetracycline, oxytetracycline and chlortetracycline should be uniformly scheduled. New Schedule 5 entries were agreed for both oxytetracycline and chlortetracycline which mirrored the Schedule 5 entry for tetracycline. The May 1998 meeting agreed to re-scheduling to Schedule 5 of those chlortetracycline, oxytetracycline and tetracycline preparations which remained in Schedule 6 on the basis that these entries presented no greater hazards than those covered by the Schedule 5 entries.

Tetracyclines inhibit bacterial protein synthesis by preventing the association of aminoacyl-tRNA with the bacterial ribosome.

## DISCUSSION

The Committee was informed that public submissions were received from XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX. These submissions were forwarded to an independent evaluator for assessment. The companies advised that they supported the retention of the current tetracycline scheduling status for the treatment of caged birds and ornamental fish and identified the follow issues as justification for this position:

- That the risk of transmission of antibiotic resistant pathogens to humans would be extremely low from the use of these antibiotics in ornamental fish and birds.
- The welfare of ornamental fish and birds will suffer because owners would be reluctant to seek veterinary advice on the grounds of cost. Furthermore, the majority of veterinarians have little expertise with ornamental fish.
- The amounts of the tetracyclines used outside Schedule 4 are very small and usually of short-term duration. Furthermore, the alternative therapies are possibly more of a risk to humans.
- A wide range of antibiotic products are available over the counter in the USA for treatment of ornamental fish and caged birds.

In accordance with new arrangements (see item 8.5), an independent assessment of the potential for the tetracyclines outside Schedule 4 to promote antimicrobial resistance was prepared by XXXXXXXXXX. Members noted the evaluation report raised the following points for consideration:

- Although resistance is widespread in many species of bacteria the class is still valuable in the treatment of some human infections.
- Uncontrolled use of tetracyclines will compromise the effectiveness of doxycycline and minocycline.

- Tetracycline resistance can compromise the effectiveness of other key human antibiotics through the process of co-selection.
- Further developments in tetracycline resistance could compromise the effectiveness of glycylyclines.
- Tetracyclines are still valuable in veterinary medicine.
- Tetracycline resistance (and resistance to other antibiotics) has emerged in aquarium fish through uncontrolled use of tetracycline.
- Disposal of water containing tetracycline resistant organisms will make an albeit small contribution to the contamination of sewage, storm water and ground water.
- Although the situation is not as clear with aviary and caged birds there is some evidence that uncontrolled use has facilitated emergence of resistant strains.
- People are at risk of resistance developing in their own bacterial flora from uncontrolled contact with tetracyclines.

On the basis of the above information, the evaluator recommended that the tetracyclines be included in Schedule 4 for all uses.

The Committee was informed that the independent assessment was forwarded to EAGAR for peer review and comment. EAGAR advised that it agreed with the reviewer's conclusion regarding the scheduling of tetracyclines and that this group of antibiotics be retained as Schedule 4. EAGAR also advised that XXXXXXXXXX abstained from commenting on the reviews provided by NDPSC.

The APVMA advised that there are 5 products containing tetracyclines outside Schedule 4. Of those identified, 3 are used in ornamental birds and 2 are pink eye treatments use on sheep and cattle. The past scheduling considerations of the products for the treatment of eye infections in cattle took into account easy availability to farmers in remote areas. The need for farmers in these areas to have ready access to these products has not changed. Furthermore, the risks posed by antimicrobials used in ornamental birds was regarded as low. Accordingly, the APVMA believes that these products should remain non-prescription products when packed and labelled for such uses.

The Committee noted that a search of the ARTG revealed that there are 17 products containing the tetracyclines.

The XXXXXXXXXX Member advised the Committee that the tetracyclines are reasonably effective against pink eye, a very painful condition that could even lead to herniation through the cornea and eventual loss of the eye. The member expressed the opinion that, if the Committee were to reschedule the tetracyclines to Schedule 4, many cases of pink eye, particularly in remote areas of the country, would remain untreated.

Members expressed the view that the quantities used in ornamental fish and birds and the overall volume of water from aquaria containing the tetracyclines released into

stormwater would not be significant. Therefore, the use of the tetracyclines in ornamental fish and birds was unlikely to increase in the potential for antibiotic resistance given the already widespread resistance seen in many species of bacteria.

#### **DECISION 2004/42 – 15**

The Committee agreed that significant uses of the tetracyclines should be restricted through inclusion in Schedule 4 of the SUSDP. Additionally, the Committee considered that the tetracyclines could be retained in Schedule 5 for ocular use in animals and the treatment of ornamental birds and fish.

#### **Schedule 5 - Amendments**

CHLORTETRACYCLINE – Amend entry to read:

CHLORTETRACYCLINE in preparations:

- (a) for topical application to animals for ocular use only; or
- (b) containing 40 per cent or less of chlortetracycline, when packed and labelled for the treatment of ornamental caged birds or ornamental fish only.

OXYTETRACYCLINE – Amend entry to read:

OXYTETRACYCLINE in preparations:

- (a) for topical application to animals for ocular use only; or
- (b) containing 40 per cent or less of oxytetracycline per dose, when packed and labelled for the treatment of ornamental caged birds or ornamental fish only.

TETRACYCLINE – Amend entry to read:

TETRACYCLINE in preparations:

- (a) for topical application to animals for ocular use only;
- (b) containing 40 per cent or less of tetracycline, when packed and labelled for the treatment of ornamental caged birds or ornamental fish only.



[Item removed]

**9. OTHER MATTERS FOR CONSIDERATION**

[Items removed]

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

No items were considered.

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

No items were considered.

## **PHARMACEUTICALS**

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

#### **12.1 PORCINE PANCREATIC ENZYMES**

##### **PURPOSE**

The Committee considered post-meeting comment from XXXXXXXXXX and XXXXXXXXXX. A late comment received from XXXXXXXXXX was also considered.

##### **BACKGROUND**

The October 2003 Meeting considered the inclusion of porcine pancreatic enzymes (PPE) in S4 of the SUSDP to effect ADEC's recommendation that PPE products be restricted to conditions characterised by pancreatic exocrine enzyme insufficiency. The ADEC was concerned of the potential risk of human infection from pancreatic enzyme products contaminated of with porcine parvovirus (PPV).

The February 2004 Meeting noted the advice from Complementary Medicines Evaluation Committee (CMEC) to the TGA that products containing PPE were suitable for use as an ingredient in listable or registrable complementary medicines. The OCM advised that PPE products were suitable for indications other than pancreatic exocrine enzyme insufficiency subject to certain manufacturing conditions to reduce the potential for PPV infectivity. Further, OCM notified the February 2004 NDPSC meeting that the Office was proceeding to consult with the Industry advising them of CMEC's recommendation and requesting the sponsor to provide the following information:

- the timeframe and the method proposed for reducing the potential of PPV infectivity in the finished product; or
- an assurance that following the agreed timeframe, companies either ensure that the manufacturing process is validated for PPV inactivation/clearance and if necessary, would introduce additional steps or obtain TGA pre-clearance.

The June 2004 NDPSC meeting, however, agreed to include all porcine pancreatic enzymes in S4 on the basis that the risk of PPV infectivity in humans was only associated with those pancreatic enzyme extracts of porcine origin. Members considered that the inclusion in S4 should ensure that all PPE preparations would be used only for the treatment of pancreatic exocrine insufficiency given that the benefits of such a use outweighed the potential risk of PPV contamination from these products.

## DISCUSSION

The Committee noted the following points raised in XXXXXXXXXX's post-meeting submission:

- The XXXXXXXXXX stated that it was inappropriate for the NDPSC to use scheduling as a mechanism for controlling the quality and safety aspects of products unrelated to the inherent safety of the substance under consideration.
- All aspects of quality were adequately managed by the TGA as part of both the Registration and Listing process and that the TGA could prevent market entry of a product that had not been certified to minimum animal disease transmission control standards. This system is actively in operation for the control of Transmissible Spongiform Encephalopathy (TSE) and there are no technical barriers to such requirements to be introduced for PPE extracts.
- XXXXXXXXXX questioned the assumption that patients “prefer to purchase the Prescription Only products as not all pharmacists stock the OTC products and that retaining such products in S4 would ensure that patients continue to access their medication under the Pharmaceutical Benefits Scheme”. This argument had presupposed that patients accessing OTC products had been doing so for pancreatic exocrine insufficiency, when CMEC recommendations had clearly stated that Listable products were not to be indicated for this purpose.
- To support scheduling on the basis of consolidation to a single access mechanism was questionable and contrary to the National Medicines Policy aims at ensuring access through simple and streamlined processes designed to avoid unnecessary administrative barriers and cost. For consumers using PPE non-prescription products, for reasons other than pancreatic exocrine insufficiency, none of these objectives had been met.
- If the NDPSC believed that there were questions regarding the evidence behind the indications other than that for pancreatic exocrine insufficiency, then proper due process would be for the TGA to conduct a formal efficacy review of these products pursuant to the legislation.

The Committee noted the following issues highlighted by OCM in its post-meeting submission:

- OCM and TGAL were concerned that inclusion of PPE in S4 could disallow the use of porcine pancreatic enzyme extracts in Listed medicines, which are free of PPV. There are mechanisms which could be put in place to provide assurance to the TGA that these products are free from porcine parvovirus (PPV), e.g. TGA Pre-clearance for animal-derived ingredients.
- OCM had written to 11 sponsors of Listed and Registered products containing porcine pancreatic enzyme extracts seeking an assurance that the manufacturing process is validated for PPV inactivation/clearance and that if necessary, additional

steps should be introduced or TGA pre-clearance be obtained. Consequently, the OCM had asked that the NDPSC set aside the scheduling decision made at the June 2004 meeting to allow an assessment of the responses received from sponsors.

XXXXXXXXXX advised that PPE had been available in a variety of XXXXXXXXXX's OTC products since before 1991. XXXXXXXXXX had indicated that it had received no reports of adverse effects but the company instead had received numerous positive feedbacks from customers with mild digestion problems. XXXXXXXXXX's current stocks of PPE-containing products was expected to last until at least April 2005, and the 1st of January 2005 implementation date of the S4 scheduling of PPE would not allow sufficient time to exhaust remaining stocks. On this basis, XXXXXXXXXX sought a reconsideration of at least the proposed implementation date, if not the basis for the initial Committee decision.

The Committee's attention was drawn to a late submission received from XXXXXXXXXX advising that pancreatin was also used in medical devices such as contact lens cleaning products. Members noted the advice from the Medical Devices Assessment Section that a contact lens cleaner solution containing PPE would be classified as a Class III device but would be exempt from the requirements of scheduling based on the Appendix A entry for medical devices (see Item 13.3).

Members noted written comment from the member expert in XXXXXXXXXX, XXXXXXXXXX and the XXXXXXXXXX Representative, XXXXXXXXXX. Both XXXXXXXXXX and XXXXXXXXXX supported setting aside the June 2004 decision to allow further opportunity for the Committee to be advised concerning the practicability of virus inactivation of PPE products.

#### **DECISION 2004/42 – 16 (Set aside DECISION 2004/41-17)**

The Committee agreed to set aside DECISION 2004/41-17 made at the June 2004 meeting to include all pancreatic enzyme extracts of porcine origin in S4, based on post-meeting comment received. (This means that the current scheduling of porcine pancreatic enzymes in SUSDP No.19 remains unchanged.) Members felt confident that the risk of PPV infectivity in humans from non-prescription medicines containing PPE could be adequately dealt with at product registration level noting that the OCM was investigating various regulatory options to help minimise the risks associated with these products, e.g. validation of manufacturing process for PPV inactivation/clearance and TGA Pre-clearance requirement.

### **12.2 KAVA AND KAVALACTONES**

#### **PURPOSE**

The Committee considered post-meeting comment from XXXXXXXXXX.

## BACKGROUND

The June 2004 Meeting agreed to include certain preparations of kava in Schedule 4 of the SUSDP based on a recommendation by the Office of Complementary Medicines (OCM) to regulate the use of kava as an ingredient in Listed Medicines. The NDPSC agreed to restrict the use of alcohol/acetone extracts of kava including those for bulk supply to health care practitioners for use in extemporaneously compounded preparations due to the potential risk of liver toxicity associated with non-aqueous extracts of kava plants at high doses. In addition, it was agreed that a schedule entry to minimise the risk without affecting the current usage of Listed complementary products should be considered by the Committee following the review of products on the ARTG.

The NDPSC 40th Meeting (February 2004) was advised that CMEC's Recommendation 41.3 had been included in Schedule 4 of the Therapeutic Goods Regulations 1990 (TG Regulations) to only allow specified concentrations of aqueous kava extracts in Listed medicines and that all other kava products had been cancelled from the ARTG. The Committee noted that the available information suggested that whole or peeled kava rhizomes and their aqueous preparations containing 250mg or less of kavalactones were acceptable for use in exempt medicines while medical advice is necessary for the safe use of other kava preparations due to their toxicity. On this basis, the Committee agreed to foreshadow the inclusion of *Piper methysticum* (kava) in Schedule 4 of the SUSDP with exemptions consistent with those specified in the TG Regulations.

The June 2004 meeting, on the grounds of public health and safety, agreed to include *Piper methysticum* (Kava) in Schedule 4 of the SUSDP, as well as adopt the exemptions specified in the Therapeutic Goods Regulations 1990.

## DISCUSSION

The Committee noted the following issues raised by XXXXXXXXXX in its post-meeting submission:

- The S4 entry for *Piper methysticum* (Kava) agreed at the June 2004 meeting removed two forms of non-prescription access to kava preparations containing kavalactones which would have been available to the consumer while still meeting the conditions for exemption from scheduling, namely:
  - all forms of kava meeting the criteria for Listable status as per the exemptions specified in the *Therapeutic Goods Regulations 1990* (the Regs); and
  - certain forms of kava not meeting the Listable status subject to a formal Registration application through the Therapeutic Goods Administration (TGA) as a non-prescription product. The NDPSC decision had eliminated an unscheduled category for kava meeting the criteria of the second recommendation, originally foreshadowed by the NDPSC at the February 2004 meeting. The recommendations of the OCM as to the criteria for Listed use of kava did not

automatically imply that all other forms must be regarded as requiring S4 status on the basis of safety.

- The original CMEC 41 recommendation for kava did not appear to have considered nor had made any recommendations as to whether preparations not included in the criteria for Listed medicines were of such a safety concern as to warrant inclusion in S4. A non-aqueous kava preparation must still undergo a full safety and efficacy evaluation as a Registered Complementary Medicine as per the criteria of the Australian Regulatory Guidelines for Complementary Medicines (ARGCM), and is able to be treated in essence like any other OTC medicine. The sponsor for such a product would have to pursue rescheduling from an S4 category through the NDPSC for any change in status.
- Kavalactones comprise a range of phytochemicals including methysticin, dihydromethysticin, kavain, dihydrokavain, demethoxyyangonin and yangonin. The use of different solvents and extraction methods would produce quantitatively different phytochemical profiles of these individual kavalactones. Such products may be able to demonstrate safety as part of the Registrable application, where the phytochemical profile of the non-aqueous extract had been tailored to minimise the content of kavalactone forms which may have a higher risk of hepatotoxicity.
- In the absence of CMEC making specific recommendations regarding scheduling, XXXXXXXXXX believed that this issue should be considered by the CMEC for advice to NDPSC prior to a decision being ratified, specifically to determine whether a case by case safety, quality and efficacy evaluation through established regulatory process for Registration was sufficient to control appropriate levels of consumer access.

Members noted that comment had been sought from OCM with regard to XXXXXXXXXX's submission. OCM stated that the CMEC recommendation to the TGA specifically identified the forms of Kava suitable for use in Listed medicines, as specified in Schedule 4 Part 4 Division 2 of the *Therapeutic Goods Regulations 1990*. OCM did not agree with XXXXXXXXXX's proposal to include "other kava preparations containing less than 250 mg kavalactones", as part of the exemption specified in the SUSDP S4 entry. Furthermore, it was advised that OCM had not specifically considered the issue relating to the scheduling of Registered products containing kava other than those forms considered appropriate for use in Listed medicines. OCM was of the view that the scheduling of such products should be determined on a product-by-product basis.

The Food Standards Australia New Zealand (FSANZ) also advised the Committee that the S4 entry agreed at the June 2004 meeting should not impact on the sale or supply of kava as a food, based on the exemption provided under Appendix A of the SUSDP for "FOOD".

Members noted that there appeared to be some confusion in the understanding of the role of scheduling vs. that of product registration. It was pointed out that determination of the scheduling of substances to restrict their supply and availability to the public is a matter

for the NDPSC, not the TGA. Conversely, scheduling does not provide a guarantee that products containing scheduled substances would be allowed on the market without the TGA's approval for registration. Additionally, the Committee considered that the proposed scheduling would allow States and Territories to regulate sole traders and extemporaneously prepared alcohol/acetone extracts of kava.

**DECISION 2004/42 – 17 (Confirmation of Decision 2004/41-18)**

In accordance with sub-regulation 42ZCZ(3) of the Therapeutic Goods Regulations 1990, the Committee agreed to confirm DECISION 2004/41-18 made at the June 2004 meeting on the grounds of public health and safety. Members considered that given the toxicity concerns on kava and in the absence of evidence to demonstrate the safety of products containing kava other than those forms recommended by CMEC as suitable for use in Listed medicines, it would be appropriate to allow the supply of such products to the public only under the advice of a medical professional.

**Schedule 4 – New entry**

PIPER METHYSTICUM (Kava) in preparations for human use **except**:

- (a) in preparations for oral use containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole or peeled rhizome when labelled with a recommended daily dose of 250 mg or less of kavalactones:
  - (i) containing more than 25 mg of kavalactones per dose, labelled with the statement:  
  
**WARNING:** Not for prolonged use. Not recommended for use by pregnant or lactating women. May harm the liver;
  - (ii) in tablet or capsule form containing 125 mg or less of kavalactones per tablet or capsule; or
  - (iii) in the form of a teabag when the amount of dried whole or peeled rhizome does not exceed 3g;
- (b) in topical preparations for use on the rectum, vagina or throat containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole or peeled rhizome; or
- (c) in dermal preparations.

### **13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS**

#### **13.1 MELIA AZEDARACH**

##### **PURPOSE**

The Committee considered the foreshadowed decision to include *Melia azedarach* in Schedule 7 of the SUSDP.

##### **BACKGROUND**

*Melia azedarach*, also called Chinaberry or White Cedar (also known in Australia as "white mahogany"), is a member of the *Meliaceae* family (not to be confused with neem, *Azadirachta indica*) and grows in subtropical areas in Asia, Australia, Hawaii, Africa, South America and parts of the southern United States. The fruit and the bark are considered poisonous and there is great variability in the symptoms seen due to genetic variation of the plant. The ingestion of as few as 6-8 berries has been fatal in some geographic locations but in other areas the fruits could be eaten without harm. Ingestion of 0.3-0.4 g of the fruit by children was reported to cause toxic reactions and 2-4 g caused death (The Complementary and Alternative Healing University website, 2003). Parts of the plant that are used for medicinal purposes are the bark, fruits, root bark, leaves and flowers.

The June 2002 meeting agreed to foreshadow the inclusion *M. azedarach* including its extracts or its derivatives in Appendix C of the SUSDP, on public health and safety grounds. Whilst the Committee recognised the need to restrict the use of *M. azedarach*, it agreed to seek additional data from stakeholders on issues such as the appropriate cut-off for exemption, long term safety of *M. azedarach* and the nature of plant extracts in products. The matter had since been considered over several NDPSC meetings but due to inadequate data the June 2003 Meeting agreed to again defer consideration to the June 2004 meeting to allow completion of a safety review on *M. azedarach* being undertaken at that time by the OCM.

The June 2004 meeting noted the OCM safety review report on *M. azedarach* and considered CMEC's recommendation that whilst the plant is not suitable for use as an ingredient in Listed medicines the NDPSC should allow continued access to *M. azedarach* by healthcare practitioners. On this basis, CMEC recommended that *M. azedarach* should not be included in Appendix C of the SUSDP. The OCM advised that the TGA would amend Schedule 4, Part 4, Division 1 of the *Therapeutic Goods Regulations 1990* to include *M. azedarach* (plant material from which herbal substances in Listable medicines must not be derived). This amendment would subsequently require medicines containing *M. azedarach* and its preparations to be individually evaluated for quality, safety and efficacy, and included on the Australian Register for Therapeutic Goods (ARTG) as Registered medicines.



The June 2004 meeting agreed not to proceed with the foreshadowed inclusion of *M. azedarach* in Appendix C of the SUSDP but foreshadowed its inclusion in Schedule 7, based on the plant's overall toxicity profile and potential for adverse effects on reproductive parameters. However, while the Committee recognised that there may be grounds for exempting medicines extemporaneously prepared by healthcare practitioners, members were unable to extrapolate from the data available to determine a safe level on which to base a cut-off for exemption to accommodate CMEC's recommendations. Consequently, the Committee asked that CMEC and XXXXXXXXXX put forward a proposal, for consideration at the October 2004 meeting, for an appropriate cut-off for the exemption of extemporaneously prepared medicines by healthcare practitioners and dilute preparations. The Committee also asked that justification be provided for any proposal for a cut-off for exemption.

## DISCUSSION

The Committee noted the Minute received from OCM advising that the August 2004 CMEC Meeting concurred with the NDPSC's view that there was inadequate scientific data available on which to base a safe cut-off level to allow the use of *M. azedarach* as an ingredient in complementary medicines.

The Committee noted that XXXXXXXXXX had not responded to the letter sent by the Secretariat dated 11 August 2004 inviting them to put forward a proposal for an appropriate scheduling cut-off to exempt extemporaneously prepared medicines by healthcare practitioners and dilute preparations.

Most jurisdictional members did not support the approach of including botanicals for human use in S7 of the SUSDP as this Schedule attracted controls in the jurisdictions not consistent with those required for human therapeutic substances. Furthermore, members were cognisant of the move towards the new Trans-Tasman agency and the need for scheduling entries related to human medicines to meet both Australian and New Zealand requirements. On this basis, the Committee agreed that it was essential to keep all human therapeutic substances within S2, S3 and S4 of the SUSDP.

However, the Committee noted that inclusion of *M. azedarach* in S2-S4 would automatically allow an exemption from scheduling requirements for preparations containing 10mg/kg or 10 mg/L of *M. azedarach* for any use, as specified under SUSDP Part 1, (2)(i), which would be contradictory to the advice received from CMEC.

## OUTCOME

On the grounds of public health and safety, the Committee agreed to foreshadow the inclusion *M. azedarach* including its extracts and derivatives in Appendix C of the SUSDP.

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**FORESHADOWED DECISION (for consideration at the February 2005 meeting)**

**Appendix C - New entry**

MELIA AZEDARACH including its extracts and derivatives.

**13.2 PSEUDOEPHEDRINE**

**PURPOSE**

The Committee considered rescheduling of the remaining Schedule 2 (S2) pseudoephedrine preparations to S3.

**BACKGROUND**

The June 2002 Meeting agreed to reschedule all OTC single-active immediate release pseudoephedrine preparations from Schedule 2 to Schedule 3 of the SUSDP on the rationale that pharmacist intervention would help reduce the problem of diversion to the illicit drug trade while maintaining access for legitimate users. However, consideration of scheduling of the remaining S2 preparations was deferred over several meetings while the NDPSC awaited the outcome of the research project to determine the extractability of pseudoephedrine from various formulations and the ease of conversion into methylamphetamine. This project was funded by the National Drug Law Enforcement Research Fund (NDLERF) at the request of the National Working Group on the Diversion of Chemical Precursors (NWG).

The NDPSC had since kept a watching brief of the remaining pseudoephedrine preparations in S2 and had taken the opportunity of asking sponsors to indicate their plans for existing and future product lines, particularly in relation to 'bilayer' preparations. XXXXXXXXXX, sponsor of XXXXXXXXXX, advised the June 2003 Meeting that there was a new compounded formulation of XXXXXXXXXX under development and that it was anticipated that a submission for this would be made to the TGA within the next 12 months. XXXXXXXXXX, another sponsor of a 'bilayer' product, advised that it had no plans of modifying XXXXXXXXXX formulation based on economic grounds, and that it did not consider this product a 'bilayer' formulation. In addition, XXXXXXXXXX indicated that the sales data for XXXXXXXXXX did not suggest that it was being targeted for diversion.

The October 2002 Meeting noted the Australian Self-Medication Industry's (ASMI) Code of Conduct, which was formally approved for implementation for a period of five years by the Australian Competition and Consumer Commission (ACCC) starting from 13 November 2003. The Code was designed to help prevent diversion of pseudoephedrine-containing medicines. Furthermore, the Pharmaceutical Society of Australia (PSA) disseminated a Code of Practice for pseudoephedrine in late 2002 to ensure that pharmacists continue to provide the most appropriate medicines and

therapeutic advice to patients without inadvertently contributing to the problem of diversion of pseudoephedrine-containing products.

The November 2003 meeting of the National Working Group on the Diversion of Chemical Precursors (NWG) noted the recent report by the House of Representatives Standing Committee on Family and Community Affairs (CFC), Road to Recovery, particularly in relation to Recommendations 82 and 83. The NDPSC February 2004 meeting noted that Recommendation 83 stated that: “the Commonwealth government amend its Standard for uniform scheduling of drugs and poisons to make all substances containing pseudoephedrine a Schedule 4 Prescription Only Medicine”. Following the February 2004 meeting, the Commonwealth’s Drug Strategy Branch was asked by the Secretariat to provide the NDPSC with the Commonwealth Government’s response to Recommendation 83 when available. Accordingly, the NWG resolved that the TGA and Customs would address the next working group meeting in relation to the CFC Report.

The June 2004 meeting noted the draft Executive Summary of the NDLERF report on the research of pseudoephedrine. It was advised that the final report was yet to be approved by the NDLERF Board of Management but it agreed that the NDPSC be provided with the Executive Summary to assist its considerations. The outcome of the research demonstrated that pseudoephedrine could be extracted from all products, with an efficiency ranging from 24%-90%, and that no significant relationship was established between product formulation, extraction process and efficiency of extraction. Eight pharmaceutical products were selected for investigation, representing the different pseudoephedrine product formulations available in Australia. The NDLERF report noted that no significant chemistry skills or sophisticated equipment was required to facilitate extraction of pseudoephedrine from any of the tested product formulations. On the basis of the findings of the research project, the Committee foreshadowed a decision to reschedule the remaining S2 pseudoephedrine preparations to S3.

Following the June 2004 meeting, the Secretariat advised in writing all stakeholders who had made a submission to the NDPSC that the above foreshadowed decision would be considered at the October 2004 meeting.

## **DISCUSSION**

The XXXXXXXXXX representative participated in the discussion via telephone.

The Committee noted the draft final NDLERF report entitled “The Extraction of Pseudoephedrine from Pharmaceutical Products” which was provided to the NDPSC for consideration. The report concluded that to reduce the risk of the diversion of pseudoephedrine containing products to the illicit drug production market, it is important to consider the full range of products available on the market and ensure that appropriate restrictions are uniformly applied to all product lines.

The XXXXXXXXXX Member provided the Committee with the minutes of the meeting of the XXXXXXXXXX Pseudoephedrine Working Group Meeting (PWG). The PWG

reported that XXXXXXXXXX was still the most popular product for diversion in XXXXXXXXXX, followed by XXXXXXXXXX and XXXXXXXXXX. However, the PWG was opposed to a blanket rescheduling of all non-prescription pseudoephedrine products to S3 and recommended that the S2 entry be amended to limit the pack size to either 5 days supply, or limit the maximum quantity per pack to say 1.2g of pseudoephedrine. Accordingly, the PWG recommended that larger packs, i.e. >5 days supply, be rescheduled to S4. The PWG was of the view that this approach should lessen the demand for pseudoephedrine for illegal purposes while maintaining the availability for legitimate consumers. The PWG also noted that this approach, however, could also increase the retail cost of products. Members noted that the minutes of the VPWG meeting also indicated that the production of false ID was becoming an ‘underground’ industry in NSW and Qld.

The XXXXXXXXXX Member put forward a proposal for the remaining pseudoephedrine preparations in S2 to be rescheduled to S3, except undivided preparations, with a recommendation to States and Territories that purchasers of ‘high risk’ products be required to present a photo ID to the pharmacist at the time of purchase.

Another jurisdictional member recalled that the October 2002 NDPSC meeting noted the information presented at a conference arranged by the Australian Bureau of Criminal Intelligence indicating that persons operating clandestine laboratories considered a 40% yield of pseudoephedrine financially viable. The member noted that the majority of products in the NDLERF report provided reasonable to high yields of methylamphetamine and that the approach of selective rescheduling to S3 of ‘high risk’ products may not offer a long term solution to the problem. It was highlighted that the available information on the drugs seized at clandestine laboratories clearly showed that the type of products targeted for diversion after single-active products were rescheduled to S3 in June 2002 shifted to combination products. Members also noted that the products selected for testing in the NDLERF report did not appear to include liquid or slow release preparations.

In a submission prior to the meeting, the XXXXXXXXXX Member supported the rescheduling of all pseudoephedrine products to S3 while recognising that scheduling alone is not the ideal mechanism for dealing with the issue of diversion. It was indicated that moving pseudoephedrine products to a schedule with more oversight by health professionals should have some impact in reducing diversion, and in addition, scheduling is a mechanism which could be implemented reasonably rapidly. Furthermore, the XXXXXXXXXX Member also suggested that further strategies to reduce the diversion of these products needed to include the following elements:

- agreement with industry to limit the number of products available and, in particular, to reduce the proliferation of combination products on the Australian market; and
- pharmacists should rationalise and reduce stock levels including the range of products held at any one location.

The Committee noted the submissions received from various stakeholders, including XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX, as well as campaign letters (29 XXXXXXXXXX submissions and 41 submissions from XXXXXXXXXX), which raised the following issues:

- The scheduling of pseudoephedrine products in S2 is appropriate on the basis of their safety profile and history of safe use. It would be inappropriate to use scheduling as a tool for addressing diversion issues. There was sufficient evidence to suggest that the initiatives, e.g. ASMI Code of Conduct and the PSA Code of Practice, which had been implemented at both the pharmacy and manufacturer level, were effective control measures which were helping to address the diversion problem. In addition, nearly 100% of pharmacies in Australia had been accredited under the Quality Care Pharmacy Program and that quality assurance protocols for managing pseudoephedrine product handling had been integral to this program. Pharmacy Assistants were also required to undergo certificate training, which included training in appropriately managing pseudoephedrine purchase requests. However, additional time would be required for all pharmacy initiatives to take a more widespread effect and the Committee should revisit this matter after a specified period to allow an assessment of the outcomes and impact of the measures currently in place to prevent diversion.
- Access by legitimate consumers to pseudoephedrine in conjunction with professional advice when required (S2) should be maintained particularly where there is no comparable alternative. Rescheduling all pseudoephedrine products to S3 would create a cost barrier for consumers and this financial detriment far outweighed any potential benefit to the community.
- There were indications that the illicit drug trade was targeting alternative sources of pseudoephedrine, e.g. break-ins, hold-ups and illegal importation, and any changes to the current scheduling would only have a minimal impact on the supply of pseudoephedrine to the drug trade. A multi-faceted, cooperative and national approach is the only mechanism that would address the problem of pseudoephedrine diversion. A range of initiatives were already in place at the local pharmacy level to manage the problem of diversion, e.g. maintaining a record of purchasers of pseudoephedrine products, stock minimisation, storage of pseudoephedrine products behind the counter, prohibitions on bonus stock to ensure the ability to trace all products containing pseudoephedrine at every stage of the supply chain, collaboration with local Police departments and general community vigilance programs. Industry, law enforcement, State and Territory governments and pharmacy groups were continuing their work in refining the approaches to the issue of diversion and were constantly trialing new initiatives.
- Photo ID to be required for purchases made by persons unknown to the pharmacist was proposed.

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- The scheduling of pseudoephedrine should be considered in the context of the Galbally Report given that a determination on S3, as a result of this report, could lead to complexity and confusion on how to handle pseudoephedrine products.
  - XXXXXXXXXX advised that it provided a complete pharmacy service throughout Australia via mail. It was indicated that whilst there had been attempts to source pseudoephedrine from XXXXXXXXXX, this issue was less of a problem with mail order than with the community pharmacy. The requirement for mail order customers to identify themselves and supply their address was considered a deterrent.
  - Most pharmacies were aware that the products targeted for diversion were the single-ingredient and antihistamine/decongestant combinations. Steps had been taken to ensure these products are kept away from direct consumer access. Formulations such as pseudoephedrine liquid preparations, e.g. cough mixtures, multiple combination and analgesic combination products with a lower ratio of pseudoephedrine such as XXXXXXXXXX and XXXXXXXXXX were considered 'low risk' products in terms of diversion to the illicit drug trade. In contrast, combination products with a higher ratio of pseudoephedrine content, e.g. XXXXXXXXXX and XXXXXXXXXX were considered 'high risk'.
  - Selective rescheduling of individual pseudoephedrine containing products would only redirect the focus of illicit-users to another S2 product. Utilising the professional integrity of pharmacists to ensure medicines are not inappropriately used is a cornerstone of the current healthcare system. Pharmacists currently ensure that the widespread misuse of prescription medicines, including narcotics, is prevented via well-controlled and monitored dispensing practices. Additionally, the fact that the medications would remain available without prescription should ensure patient access to these safe and efficacious medicines.
  - The percentage of pharmacy-bought products diverted relative to sales was low and the sales volume of all pseudoephedrine products was decreasing, therefore, rescheduling of the remaining products in S2 was not warranted.
  - Community pharmacies would not be able to support the requirement for extra professional staff to personally oversee the sale of every pseudoephedrine product during peak cold/flu season. An estimated 6 million units of pseudoephedrine products were sold annually, with peak sales of more than half a million units per month during the peak season (May-November). XXXXXXXXXX indicated that an average of 40 pseudoephedrine packs per day was sold under trained pharmacy assistant supervision. If all S2 pseudoephedrine products were moved to S3, this would mean that an extra 2 hours a day would be spent by the pharmacist dispensing pseudoephedrine, which is time taken away from the provision of professional counselling to consumers. To avoid this problem, more pharmacies may choose not to stock pseudoephedrine products which would limit the availability to consumers of an effective medicine for the symptomatic relief of nasal congestion.
  - Some consumers would find the involvement of professional staff in routine OTC sales to be intrusive and may choose not to seek treatment altogether or turn to other

more easily accessible products such as topical nasal decongestant which are associated with side-effects such as rebound congestion and nose bleeds.

- The XXXXXXXXXX opposed the S3 rescheduling proposal and raised three main concerns in its late submission:
  - There is a lack of consistency in poisons regulation and professional controls in the jurisdictions. States and Territories do not have uniform controls and requirements for the supply of S3 and S2 medicines to consumers, e.g. storage, labelling, reporting and recording requirements. In an attempt to curb the amount of pseudoephedrine being diverted to the illicit market, additional guidelines and protocols for the handling of pseudoephedrine had been developed by professional bodies such as PGA, PSA and the Pharmacy Boards in each state. These protocols and guidelines, which specify storage and labelling requirements, reporting, as well as the degree of personal intervention required by the pharmacist, would add to the lack of uniformity in the supply of pseudoephedrine containing products across Australia.
  - There appears to be a lack of national data on the patterns of diversion to determine the impact of regulatory and professional control measures, and assess the need for modifications to control measures that impact on a particular part of the pseudoephedrine and precursor chemicals supply chain. XXXXXXXXXX had received conflicting advice about the level of diversion to the illegal manufacture of amphetamine from different parts of the supply chain. Nationally aggregated data regarding police seizures of pseudoephedrine could not be obtained to assist in determining the points of diversion, e.g. purchase from a community pharmacy, stolen from pharmacies and stolen/diverted from wholesalers. In addition, there is a need to determine the level of diversion of S2 products from mail order or Internet pharmacies. Currently, there is a potential for bulk purchases of pseudoephedrine containing products without question from Internet pharmacies. Whilst some sites defaulted to 1 pack when multiple packs are requested from Internet pharmacies, it appeared that multiple single purchases could be made on any given day. If this is correct then the XXXXXXXXXX would recommend tightening of restrictions on Internet pharmacies to close this loophole and limit the diversion of these products. The XXXXXXXXXX could not support further regulation without data supporting the need for further control on the community pharmacy component of the supply chain.
  - The XXXXXXXXXX would not support controls that could hinder access by consumers with a genuine therapeutic need and the compliance with new regulatory requirements for pseudoephedrine products would result in increased cost for consumers. There were approximately 140 different brands of pseudoephedrine products in S2. The XXXXXXXXXX was concerned that the vast majority of genuine consumers would pay a price for extra regulation of all these products in an attempt to decrease the overall small minority of people who access pseudoephedrine for illicit purposes. A higher level of regulation such as one requiring the involvement of the pharmacist in every supply would

- significantly impact on the workload of community pharmacists (extra 1.5 hours each day based on 3 minutes of pharmacist time per sale) and adversely affect the health service provided by pharmacists.
- The XXXXXXXXXX opposed the proposal and raised a range of issues which included the following:
    - The level of vigilance associated with the handling of S2 pseudoephedrine-containing products in the community pharmacy sector was already addressed in the PSA's Code of Professional Conduct. The Code, which was distributed to the profession in late 2002, provided substance-specific guidance to pharmacists, taking into consideration the current environment of use and patterns of misuse.
    - It had been reported at a national forum [National Working Group on the Diversion of Chemical Precursors (NWG), Meeting of 12 August 2004] that the diversion of pseudoephedrine from the community pharmacy sector accounted for about 15% of the total amount diverted to the illicit manufacture of amphetamine-type substances. Whilst initiatives were being implemented at national and state levels to prevent the diversion of pseudoephedrine and other precursor chemicals, it was clear that the strategies to address other sources of diversion (accounting for the remaining 85%) needed to be developed. Pharmacists were constantly being reminded of their professional duty of care in detecting, monitoring and minimising problems of misuse and diversion. However, pharmacists also operate in an environment where this role must be balanced against their need to ensure patients with a genuine clinical need have access to professional advice and treatment for self-limiting or minor ailments.
  - The XXXXXXXXXX submission had raised similar concerns as the XXXXXXXXXX and had urged the NDPSC to take into account the positive outcomes of ongoing and collaborative activities being undertaken at the community pharmacy level to address the problem of diversion. The following additional points were highlighted by XXXXXXXXXX for consideration:
    - Industry had decided to extend the prohibition on bonus stock to all pseudoephedrine-containing products. Previously, only single entity products were subject to this prohibition but an amendment to the Code of Conduct would ensure traceability of all pseudoephedrine-containing products at every stage of the supply chain.
    - XXXXXXXXXX would address the issue of in-store theft in collaboration with the XXXXXXXXXX and the XXXXXXXXXX by encouraging participating companies to assist pharmacists in re-positioning stock to minimise the risk of theft.
    - A survey of all sponsors who marketed pseudoephedrine combination products confirmed that there were no products on the market containing more than 10 days supply when taken as directed.
    - The XXXXXXXXXX Pseudoephedrine Team, which included all manufacturers and sponsors of pseudoephedrine-containing products, whether XXXXXXXXXX



- members or not, agreed at a meeting in August 2004 to develop and run an on-going awareness campaign in the pharmacy 'trade' press in order to raise and maintain awareness of the potential for pseudoephedrine products to be diverted.
- More recent data supplied to XXXXXXXXXX showed a steady reduction in sales of pseudoephedrine products, which supported the contention that the combined effects of the various initiatives implemented were beginning to produce results.
  - Removing pseudoephedrine products from S2 would further disadvantage consumers in rural and remote areas where pharmacy services are not available and only S2 products could be sold under these circumstances.
  - Industry and pharmacy activities such as the implementation of the Industry Code of Conduct, raising and maintaining awareness about the diversion potential of pseudoephedrine products, collaborative work between pharmacists, Police and Industry as well as participation in National Activities were helping to reduce the sales of pseudoephedrine products.
- The XXXXXXXXXX supported the rescheduling proposal due to the increasing problem of diversion of pseudoephedrine to the illicit drug market. The XXXXXXXXXX believed that pharmacist intervention should aid in the reduction of this problem while maintaining access by legitimate consumers.
  - The XXXXXXXXXX provided a late submission raising a number of issues including the following:
    - The rescheduling of single active pseudoephedrine tablets from S2 to S3 in June 2002 (effective 1 January 2003) had caused a dramatic shift in the products targeted for diversion, i.e. from single active to combination tablets. This evidence was based on seizures from illicit methylamphetamine laboratories, arrested 'pseudo runners' and pharmacy intelligence.
    - In 2003, fifty (50) clandestine drug laboratories were seized and dismantled by the XXXXXXXXXX. Ninety five percent (95%) of these laboratories were involved in reduction reactions converting pseudoephedrine to methylamphetamine. Almost all these laboratories had used pseudoephedrine extracted from 'cold & flu' tablets obtained from community pharmacies. The following reasons were suggested as to why combination products were being targeted for diversion :
      - Identification was rarely requested or the purchase questioned by pharmacy staff;
      - Some combination tablets contained high quantities of pseudoephedrine (120 mg) and the ease of extraction was no more difficult than that of single-active products;
      - A wider variety of brands are available including an increase in generic brands; and
      - These products were displayed on pharmacy shelves (not behind the counter) and the opportunity was present for products to be stolen (shoplifted).

- The incidence of clandestine manufacture of methylamphetamine did not appear to be easing and detections in NSW had consistently increased over the past decade. Whilst the scale and capacity of drug laboratories vary in NSW, analysis of these seizures showed the proportion of smaller portable labs processing pseudoephedrine tablets acquired locally was increasing.
- Many examples had been compiled which demonstrated the flexibility of organised criminal groups. The development of identified 'pseudo running' networks revealed that such groups were willing and capable of circumventing existing regulations regarding the handling and supply of pseudoephedrine based products. The table below shows the shift in percentage of single actives to combination tablets over the last 5 years, based on samples seized from illicit drug laboratories where the yearly totals varied between 65,000 and 300,000 tablets (it was acknowledged that this quantity of actual seizures had no real relationship with the actual quantity of diversion occurring).

2000: 07% combination tablet

2001: 12% combination tablet

2002: 83% combination tablet

2003: 86% combination tablet

2004: 94% combination tablet

- Further analysis of 2003 seizures revealed that there were sixty one (61) interventions of 'pseudo runners' in NSW. As a result of those interventions, a total of 5,583 pseudoephedrine-based tablets were seized. Of this amount, only 210 (3.7%) were single active tablets. This regional snapshot also reflected the statewide S3 scheduling of single active tablets arguably effective in deterring criminals from targeting such products. A statewide 'pseudo runner' arrested in October 2003 resulted in 7716 tablets seized in which only 2% were single active tablets.
- Recent hearings conducted by the Amphetamine and Other Synthetic Drugs Determination, Australian Crime Commission, had identified by way of interview with industry experts that overseas markets, particularly the UK, had established an alternative medication to pseudoephedrine with no identified risk of illicit diversion, i.e. phenylephrine. Although the efficacy levels of this active ingredient was not agreed upon by the Australian pharmaceutical industry, phenylephrine had been the subject of overseas research as an alternative to pseudoephedrine. A product shift to phenylephrine by manufacturers may provide an alternative S2 product should the remaining S2 pseudoephedrine products be rescheduled.
- XXXXXXXXXX recommended that the proposed rescheduling of the remaining 'combination' pseudoephedrine products to S3, where there is a compliance capacity, be supported due to the current and future risks of organised criminal diversion into the illicit drug manufacture. Both slow release preparations and

pseudoephedrine/antihistamine combination products have evidence of being ‘high risk’ products for criminal diversion.

- Treaties and Monitoring advised that the pseudoephedrine import totals for the year 2002, 2003 and 2004 (as at 27/9/2004) were as follows:

2004: 5,979 kg  
2003: 13,143 kg  
2002: 17,277 kg

The Australian pseudoephedrine import totals for the years 1997-2001 were as follows:

2001: 20,644,000  
2000: 16,101,375.844  
1999: 18,739,060.616  
1998: 11,469,471.035  
1997: 26,905,932.512

A member noted that a common issue highlighted in the submissions received was the perceived ‘inappropriateness’ of using scheduling as a tool for addressing the problem of diversion. However, it was highlighted that one of the matters to be taken into account by the Committee in exercising its power, as specified under section 52 E of the *Therapeutic Goods Act 1989* (TG Act), is the potential for abuse of a substance.

It was highlighted that the detection of clandestine laboratories manufacturing methylamphetamine in both NSW and Queensland had consistently increased over the years. Additionally, information provided to the Committee indicated that there has been a shift to combination pseudoephedrine products for diversion to the illicit drug trade following the reclassification of single active products to S3.

The XXXXXXXXXX Member advised that the NSW Poisons Advisory Committee (NSWPAC) had considered the matter on 5 October 2004. It was agreed that a number of voluntary measures be implemented as an alternative to reclassifying combination pseudoephedrine products to S3. It was noted that if the voluntary measures failed to prevent diversion of pseudoephedrine, then these products would be reclassified to S3 in June 2005.

The Committee noted that the problem of pseudoephedrine diversion was not an issue in the UK because phenylephrine was being used in place of pseudoephedrine as decongestant in products. Members considered that this approach could provide a long term solution to the problem and agreed that manufacturers should be encouraged to develop new formulations using phenylephrine as an alternative decongestant instead of pseudoephedrine.

The Committee was advised that the Commonwealth Government's response to Recommendation 83 of the 'Road to Recovery' report was yet to be made available by the Commonwealth's Drug Strategy Branch.

## **OUTCOME**

The Committee agreed to take no scheduling action at this time to provide additional time for the initiatives implemented by government, industry and pharmacy organisations to take full effect but resolved to continue monitoring the problem of diversion of pseudoephedrine. The Committee indicated that it was willing to consider rescheduling all pseudoephedrine-containing products to S3 or S4 in the future, if the diversion problem remained unresolved. In the interim, the Committee agreed to make the following recommendations:

- All pharmacy organisations and ASMI should implement specific guidelines and requirements for all community pharmacists to take the necessary precautionary measures to minimise the potential for pharmacies to be targeted as a source of pseudoephedrine for diversion. Such measures should include reduction in stock holdings and range of products kept in the premises and relocation of pseudoephedrine products to an area in the pharmacy not open to self-selection by the public.
- All jurisdictions should enforce any mandatory requirements for all S2 pseudoephedrine products to be made not accessible for self-selection by the public; and
- Request the TGA to facilitate the registration of new products containing phenylephrine as the decongestant in place of pseudoephedrine.

## **13.3 MEDICAL DEVICES**

### **PURPOSE**

The Committee considered the foreshadowed decision to include an entry in Appendix A of the SUSDP to exempt certain medical devices from the requirements of scheduling.

## BACKGROUND

The NDPSC 31st Meeting (May 2001) agreed that a strategy for medical devices containing scheduled poisons needed to be developed to achieve meaningful public health outcomes in terms of labelling and controls over access and availability of such devices. The Committee recognised the need for a clear and positive statement in the SUSDP to resolve the general confusion in terms of when a device containing a medicine required scheduling. This matter was considered over several meetings of the NDPSC and was subsequently deferred to a future meeting to allow sufficient time to examine the new device classification listing.

The *Therapeutic Goods Amendment (Medical Devices) Act 2002* came into effect in October 2002 and representatives from the Medical Devices Assessment (MDA) area provided the February 2003 meeting with a brief overview of the new legislation. The new regulatory regime for medical devices adopts a classification system that has currently 5 classes of medical devices under this system. From these, MDA developed a list of Class III ECRI medical devices which may require scheduling on the basis that they may contain scheduled substance(s) and were likely to be used outside the hospital or medical setting.

The June 2004 meeting endorsed an Appendix A entry which exempted Class III medical devices containing scheduled substances considered to be of low abuse or misuse potential on the basis that such devices were used exclusively within the hospital or medical setting. In addition, it was also agreed that the Appendix A entry should specify the group of medical devices which are not appropriate for exemption, e.g. disinfectants, injectable collagen or tissue reconstructive materials, rather than just provide a 'blanket' exemption. It was noted that further amendments to the Appendix A entry could be made on a case-by-case basis via the usual NDPSC procedures, where appropriate. The meeting also agreed that the NDPSC be provided with future MDEC minutes to allow identification of medical devices, which may be of interest to the NDPSC.

## DISCUSSION

The Committee noted the advice that the Medical Devices Group (MDG) suggested the foreshadowed Appendix A entry with a proposal for minor amendments to the wording. Likewise, it was noted that the TGA's Legal Services Group endorsed the foreshadowed Appendix A entry with a proposal for a minor amendment to the wording.

The Committee also noted the submission from XXXXXXXXXX raising the following points:

- Artificial tears should be included in the Appendix A exemption as it is only in very exceptional circumstances that an artificial tear product would be classified as Class III according to the rules set out in Schedule 2 of the Therapeutic Goods (Medical Devices) Regulation 2002. An artificial tear would only be included in Class III if it contained an ingredient of animal origin. The "normal" classification for an artificial

tear product would be Class IIb (if the labelling contained claims about use with contact lenses) or Class I sterile. On this basis, it was recommended that the reference to artificial tears be removed from the list of exceptions proposed for the new Medical Devices entry and that a separate entry should be included in Appendix A specifically for artificial tears.

- Schedule 4 substances which were commonly used for cosmetic procedures such as hyaluronic acid, hyaluronan, sodium hyaluronate, collagen, polylactic acid and polyacrylamide, could potentially become unscheduled.

MDA was asked to comment on XXXXXXXXXX's submission and the following points were noted in MDA's response:

- Artificial tear products currently on the ARTG are exempt from scheduling requirements and are not covered by the proposed new Appendix A entry because they are not classified as Class III. Artificial tears only become Class III if they contain material of animal or microbial origin, or if they contain a medicine, such as an antibiotic. If artificial tear preparations contain a medicine, MDA recommended that scheduling requirements should be applied.
- MDA agreed with XXXXXXXXXX in that substances such as hyaluronic acid, collagen, polylactic acid and polyacrylamide, remained appropriately scheduled and should not be made exempt under the new Appendix A entry for medical devices. MDA indicated that the Appendix A entry it had proposed to the NDPSC, whilst it excluded all such substances, did not include a prescriptive list of all injectable tissue reconstructive, augmentation and restoration materials to allow coverage of new materials for similar use which may emerge in the future.

## **DECISION 2004/42 – 18**

The Committee agreed to include in the SUSDP an Appendix A entry to exempt certain medical devices from the requirements of scheduling and confirmed that the specified exclusions to this entry were for medical devices containing scheduled substances which the Committee wished to remain subject to scheduling requirements, where appropriate.

In addition, the Committee reaffirmed its view that further changes to the Appendix A entry would be considered on a case-by-case basis according to the procedures set out in the Guidelines for NDPSC.

### **Appendix A - New entry**

MEDICAL DEVICES classified as Class III by the classification rules set out in Schedule 2 to the Therapeutic Goods (Medical Devices) Regulation 2002, as in force from time to time, **except**:

- (a) injectable tissue reconstructive, augmentation and restoration materials, including collagen;

- (b) medical devices which include anticoagulants;
- (c) artificial tears;
- (d) urinary catheters; or
- (e) intra-articular fluids.

### **13.4 ASPIRIN**

#### **PURPOSE**

The Committee considered the foreshadowed decision to amend the Schedule 2 entry for aspirin to take into account the revised Reye's Syndrome warning statement proposed by MEC.

#### **BACKGROUND**

Reye's Syndrome was first described in 1963. Reye reported on a series of 21 children admitted to the Royal Alexandra Hospital for Children in NSW over the period 1951-1962, with acute encephalopathy and fatty changes in the liver. Similar cases were reported in the USA and the UK, mostly in association with use of aspirin. Reye's Syndrome generally presents as pernicious vomiting following a viral illness. Encephalopathy subsequently occurs, often as hyperexcitability which may progress to coma and death.

The MEC February 2004 meeting has recommended to the NDPSC that it amend the warning statement for aspirin in the SUSDP based on the outcome of the review which investigated the link between aspirin intake in children and Reye's Syndrome. This review was undertaken in response to regulatory actions recently undertaken by both the UK and the USA requiring stronger warning statements regarding Reye's Syndrome on product labels. The June 2004 NDPSC meeting endorsed the revised aspirin warning statement proposed by MEC and foreshadowed a decision to amend the SUSDP Schedule 2 and Appendix F entries for aspirin at the October 2004 meeting.

#### **DISCUSSION**

The Committee noted that no pre-meeting submissions were received in relation to this matter.

#### **DECISION 2004/42 – 19**

The Committee agreed to amend the Schedule 2 and Appendix F, Part 1 entries for aspirin in the SUSDP to include a Reye's syndrome warning statement for non-prescription aspirin products on the grounds of public health and safety.

## Schedule 2 - Amendment

ASPIRIN - amend entry to read:

ASPIRIN **except**:

- (a) when included in Schedule 4, 5 or 6;
- (b) in individually wrapped powders or sachets of granules each containing 650 mg or less of aspirin as the only therapeutically active constituent other than an effervescent agent:
  - (i) when enclosed in a primary pack that contains 12 or less such powders or sachets of granules;
  - (ii) when the primary pack is labelled with warning statements to the following effect:

Don't use [this product / name of the product]:  
If you have a stomach ulcer  
In the last 3 months of pregnancy  
If you are allergic to aspirin or anti-inflammatory medicines;

Unless a doctor has told you to, don't use [this product / name of the product]:  
For more than a few days at a time  
With other medicines containing aspirin or other anti-inflammatory medicines  
If you have asthma  
In children under 12 years of age  
In children 12-16 years of age with or recovering from chicken pox, influenza or fever  
If you are pregnant;

See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. [Can be omitted in products for inhibition of platelet aggregation.];
- (c) in tablets or capsules each containing no other therapeutically active constituent **other than** an effervescent agent when:
  - (i) packed in blister or strip packaging or in a container with a child-resistant closure;



- 
- (ii) in a primary pack of not more than 25 tablets or capsules, each containing 325 mg or less of aspirin, or in a primary pack of not more than 16 tablets or capsules, each containing 500 mg or less of aspirin; and
  - (iii) the primary pack is labelled with warning statements to the following effect:

Don't use [this product / name of the product]: If you have a stomach ulcer  
In the last 3 months of pregnancy  
If you are allergic to aspirin or anti-inflammatory medicines;

Unless a doctor has told you to, don't use [this product / name of the product]:  
For more than a few days at a time  
With other medicines containing aspirin or other anti-inflammatory medicines  
If you have asthma  
In children under 12 years of age  
In children 12-16 years of age with or recovering from chicken pox, influenza or fever  
If you are pregnant;

See a doctor before taking [this product / name of the product] for thinning the blood or for your heart. [Can be omitted in products for inhibition of platelet aggregation.]; or
- (d) in tablets or capsules each containing no other therapeutically active constituent **other than** an effervescent agent when:
- (i) packed in blister or strip packaging or in a container with a child-resistant closure;
  - (ii) in a primary pack containing 100 or less tablets or capsules, each containing 100 mg or less of aspirin when packed and labelled for the prevention of cardiovascular disease or for the inhibition of platelet aggregation; and
  - (iii) the primary pack is labelled with the warning statement to the following effect:

For use under medical supervision only.

## **Appendix F, Part 1 – Amendment**

Warning Statement 102 – amend entry to read:

102. Unless a doctor has told you to, don't use [this product / name of the product]:  
For more than a few days at a time  
With other medicines containing aspirin or other anti-inflammatory medicines  
If you have asthma  
In children under 12 years of age  
In children 12-16 years of age with or recovering from chicken pox, influenza or fever;  
If you are pregnant.

## **Appendix F, Part 3 – Amendment**

### **Poison**

### **Warning Statements**

Aspirin – amend entry to read:

Aspirin

- (a) for inhibition of .....36  
platelet aggregation.
- (b) in sustained release .....36  
preparations containing  
650mg or more of aspirin.
- (c) in other preparations.....101, 102 and 103

## **13.5 KETAMINE**

### **PURPOSE**

The Committee considered the proposal to reschedule ketamine from Schedule 4 (S4) to Schedule 8 (S8).

### **BACKGROUND**

Ketamine [2(2-chlorophenyl)-2-(methylamino)-cyclohexanone], is an arylcycloalkylamine structurally related to phencyclidine (PCP) and cyclohexamine. Ketamine has clinical applications in both human and veterinary medicine and is a rapidly acting, relatively safe parenteral analgesic and anaesthetic agent that has been in clinical use since 1970.

The June 2004 NDPSC meeting was advised that the March 2004 National Working Group on the Diversion of Chemical Precursors (NWG) considered the issue of misuse and diversion of ketamine. At this meeting, the NWG noted that the therapeutic use of ketamine had been increasing from that as a human and veterinary anaesthetic to analgesic in palliative care and emergency medicine for use by medical practitioners and dentists. However, the NWG was advised that there was growing evidence of illicit use of ketamine due to its psychotropic effects and that the substance had been found in either its pure form or in combination with other substances such as MDMA [N,(-dimethyl-3,4-(methylenedioxy)phenylethylamine)].

The NWG noted that ketamine was not easily synthesised and therefore the supply to the illicit drug market was most likely through diversion of pharmaceutical products from various points in the supply chain and through importation. The NWG also noted that some jurisdictions had increased the storage and reporting requirements for ketamine in health services, however, the working group considered such initiatives may be inadequate to cover all diversion points. The loss of ketamine shipments and procurement of unreasonably large quantities of ketamine by certain individuals had also been reported.

The June 2004 NDPSC meeting was advised, that due to the problem of diversion of the substance to the illicit drug trade, the NWG would be seeking the rescheduling of ketamine at the October 2004 meeting.

## DISCUSSION

### Key Issues

The Committee received a submission from the NWG seeking the rescheduling of ketamine from S4 to S8. The Committee noted that the proposal to reschedule ketamine had been Gazetted and public comment had been received.

The Committee confirmed that there were currently 2 products registered on the ARTG containing 200mg/2mL ketamine (as hydrochloride) injection ampoule. Both are recommended for use as anaesthetic agent for diagnostic and surgical procedures. The PUBCRIS listed 7 veterinary medicines containing ketamine (87-100 mg/mL) for use in anaesthesia.

The NDPSC noted that ketamine's potential for abuse had been known for over 30 years. Street use of ketamine solutions was first observed in the US in 1971. During the 1980's a wide range of illicit ketamine preparations became available in the US including capsules, powder, crystals, tablets and solutions in addition to the licit injectable forms. The non-medical use of ketamine had increased over the last 15 years, linked with the growth of the dance culture and alternative spirituality movement.

There have been few deaths by pure ketamine overdose recorded. Of the 87 ketamine-linked deaths in New York City (up to 2000), none was purely due to the use of ketamine.

The majority of deaths associated with ketamine misuse were due to the dangerous activities or contexts of its use. In considering ketamine and public health, the Committee noted a paper by Copeland and Dillon from the National Drug and Alcohol Research Centre, University of New South Wales [Copeland. J., Dillon P., **“Ketamine and Public Health”** (undated but prepared post 2003)] which concluded that “as levels of ketamine in the general population are very low, the harms reported by recreational users are not excessive and the mortality rate is low, ketamine does not appear to pose a risk to public health at this time.” Copeland and Dillon suggested that the harms that require further investigation are those associated with unsafe sex, injecting behaviours, neurotoxic effects and use in situations where there is heightened risk of accidental death.

The Australian Illicit Drug Report (AIDR) 2001-2002 produced by the Australian Crime Commission noted that ketamine was difficult to manufacture and its precursor chemicals were not easily available. Consequently, the drug was probably not clandestinely produced and therefore the majority, if not all, illicit ketamine was being diverted from legitimate medical or veterinary sources. The report also noted that ketamine had the potential to be both physically and psychologically addictive.

The Committee noted that the NWG Report summarised the issues relating to ketamine and illicit use as follows:

- The schedule 4 drug ketamine is a widely used anaesthetic agent in medical practice (with increasing use as an analgesic in palliative care and emergency medicine), dental practice and particularly in veterinary practice.
- Ketamine’s dissociative properties have resulted in the potential for misuse and illicit recreational use increasing across Australia (commonly found combined with other “party drugs” or sprayed on amphetamine-type “pills”) with low doses giving an “ecstasy-like” effect.
- Overdose is rarely the sole cause of ketamine-related deaths in Australia. More commonly accidents occur while taking the drug, and there is a potential for ketamine, like GHB, to be used in sexual assaults as a “date rape” drug.
- Unlike many illicit substances, ketamine is difficult to manufacture and precursors not easily obtained. There have been no reports of local illicit manufacture and therefore the source is primarily from importation or diversion from medical, dental and veterinary supplies.
- Ketamine is sold on the illicit market in liquid, tablet or more commonly powder form, which is produced by simple evaporation of liquid ketamine and grinding of the resultant crystals.
- There are reports of diversion from hospitals and veterinary surgeries.

- Recently Victorian Police have reported that the major source of illicit ketamine in that State is thought to be arising from diversion of veterinary preparations from the greyhound and horse-racing industries.
- In December 2003, advice to the New Zealand Expert Advisory Committee on Drugs relating to ketamine highlights the increase risk posed by ketamine and proposed that ketamine be classified as a Class B1 controlled drug, as is morphine.
- There is increasing evidence of dependence among recreational users of ketamine.

#### Australian Experience

In regard to current Australian experience, the Committee noted advice that the NWG had been advised that the Australian Federal Police in the ACT had observed a trend of spraying methamphetamine-containing tablets with ketamine to produce an initial “ecstasy-like” effect. Purchasers believed they were therefore buying pure ecstasy tablets (AIDR 2001-02). Furthermore, anecdotal reports of police seizures and clandestine laboratory investigations in South Australia indicated that ketamine was associated with methamphetamine production but without clearly identified sources. Recently, the Victorian Police had reported that the major source of illicit ketamine in that State arose from the diversion of veterinary preparations from the greyhound and horse-racing industries. It had been the official view in the past that the illicit use and availability of ketamine in Australia was low and agencies rarely came into contact with it (AIDR 2000-01). However, Australian law enforcement agencies were now becoming more concerned, particularly as evidence showed that recreational use was increasing and ketamine was being used in sexual assaults (AIDR 2001-2). A Committee member noted that at times legitimate supplies of ketamine were difficult to obtain due to the level of diversion for unlawful purposes. A member reported that the Western Australian police that the amount of ketamine seized was far greater than would be accounted for by reports of ketamine being stolen from veterinary surgeries and it was likely that quantities of ketamine were also being imported.

While ketamine was not considered to be one of the major drugs of misuse in Australia, (unlike heroin, ecstasy and methamphetamine), the source of the drug could be narrowed down to diversion of licit pharmaceuticals from the health professions and importation from overseas. Issues surrounding the diversion from health professionals were the responsibility of governing bodies through drugs and poisons legislation.

#### Proposal for Rescheduling to Schedule 8

In proposing that the NDPSC consider rescheduling ketamine to Schedule 8, the Working Group noted that the NDPSC guidelines describe a Schedule 8 substance as one that is for therapeutic use which is dependence producing or likely to be abused or misused. The assessment factors were inclusion in Schedule I or II of the WHO Single Convention on Narcotic Substances, Schedule II or III of the WHO Convention on Psychotropic Substances or was likely to present a substantial risk of abuse, dependence or misuse for

illegal purposes. It was noted that there was growing evidence of the physical and psychological symptoms of ketamine dependence among recreational users. A withdrawal syndrome, including psychotic features, was also beginning to be described.

The Working Group also noted reference to the fact that, while ketamine was not currently under international control, the WHO Expert Committee on Drug Dependence had recently found that there was sufficient information available to justify the scheduling of the substance under the United Nations drug control conventions and had thus initiated a full critical review of ketamine.

#### Response to the Pre-Meeting Gazettal

In response to the NDPSC's Gazettal of the proposal to consider the rescheduling of ketamine, the Committee received comment from XXXXXXXXXX, XXXXXXXXXX and XXXXXXXXXX. All opposed rescheduling of ketamine from S4 to S8.

The XXXXXXXXXX believed that rescheduling would create unfair and unnecessary difficulties for manufacturers and distributors of veterinary medicines. These difficulties included handling and storage problems, particularly for equine veterinarians where the drug is used extensively in the field. In addition, it was claimed that in Victoria there would be additional imposts on distributors and/or wholesalers where a doctor, pharmacist or dentist was required to be employed full-time on staff to ensure appropriate storage, ordering and transport controls. However, the XXXXXXXXXX representative noted that this was not quite the case. In Victoria, it was only necessary for distributors/wholesalers supplying Schedule 8 substances to employ staff that had tertiary science training or 5 years experience or training in the handling of drugs. Such trained staff were only required to be present when transactions took place.

The XXXXXXXXXX also expressed the view that rescheduling ketamine would only increase the attractiveness to the clandestine drug market, raise the price of the material and make it more profitable and therefore more attractive to criminals. XXXXXXXXXX noted that, in their discussions with the Australian Crime Commission, the Commission had indicated that it would be prepared to consider possession of the drug without lawful excuse to be a crime thereby allowing the continued legitimate manufacture of ketamine for veterinary use while at the same time giving law enforcement authorities a satisfactory mechanism to deal with illicit supply and use. However, the Committee noted that it was already an offence in all jurisdictions to possess ketamine without lawful excuse. However, despite this, illegal sale had continued.

The XXXXXXXXXX also did not support the rescheduling of ketamine, noting that in the case of ketamine, rescheduling was an inappropriate mechanism as it was not a drug of addiction. The XXXXXXXXXX drew analogies with the diversion of steroids where the problem was satisfactorily addressed through supply controls on veterinary surgeons and additional record keeping requirements that were subject to audit. XXXXXXXXXX had issued warnings to its members regarding diversion to the illicit drug trade and the need

for vigilance and security. XXXXXXXXXX also requested the NDPSC to defer a decision to a subsequent meeting so as to allow more time for the XXXXXXXXXX to develop a full submission. The Committee noted that the XXXXXXXXXX would have the opportunity to make a further submission should the Committee decide to make a scheduling amendment in relation to ketamine.

XXXXXXX noted the relative safety of the drug and that the main dangers associated with ketamine use were likely to stem from the context of use rather than the direct physical harms of the drug. XXXXXXXXXX also noted that over the last few years, a number of controls had been imposed to address the illicit use of the drug, including the requirement of a permit to import ketamine, a change in the law to allow the prosecution of individuals possessing ketamine and the listing of ketamine under the New South Wales *Drug Misuse and Trafficking Act 1985*, ensuring that tougher penalties were in place to deal with its illicit use. If ketamine use was on the rise as stated by NDPSC, then XXXXXXXXXX questioned where the root of the problem resided.

XXXXXXX also considered that the proposal to reschedule ketamine was likely to have an impact on the legitimate medical and veterinary use or possession of the drug, such as imposing additional requirements of accountability and storage. Furthermore, rescheduling would impose an additional control on the finished product rather than the active drug substance, which XXXXXXXXXX understood to be preferred by the illicit drug market. XXXXXXXXXX questioned whether targeting the illicit attainment of finished ketamine product via the medical distribution channels where there were already levels of control, was likely to have a significant impact. The NDPSC understood however, that the focus of the illicit trade was in finished product and not the unformulated active ingredient.

XXXXXXX considered that the NDPSC should give consideration to whether an alternative control that targets the active substance rather than the finished product would be more effective in eradicating illicit use. The company also considered that while the import permit monitored entry of ketamine into Australia, the subsequent distribution of the substance was not monitored on a national basis. It was also suggested that there should be further investigation of the diversion of large quantities of ketamine before imposing additional controls on the use of ketamine by the medical community.

#### Appropriateness of Rescheduling

While the illicit use of ketamine was of concern, rescheduling as a control measure had been questioned. However the Committee agreed that rescheduling could be an effective approach to countering illegal drug supply.

In respect to veterinary use, the representative of the XXXXXXXXXX indicated that the APVMA would be able to give regulatory effect to the decision if a Schedule 8 classification was proposed. The representative did note, however, that ketamine was also used in the develvetting of deer which may be adversely affected by a Schedule 8

classification. The XXXXXXXXXX representative was asked and confirmed that veterinary ketamine was supplied in 50ml, multi-dose vials. This form of product presentation was consistent with large-scale veterinary use and also for use with large and possibly exotic animal (zoo) species.

Both New Zealand and Australian authorities had noted a rise in ketamine use, particularly as a 'party drug' by young people. Additionally, New Zealand had noted that there was growing evidence of physical and psychological symptoms of ketamine dependence among recreational users. A withdrawal syndrome, including psychotic features, was also beginning to be described.

#### **DECISION 2004/42 – 20**

The Committee agreed to reschedule ketamine from Schedule 4 to Schedule 8 on the basis of the available information which suggested increasing illicit use and evidence of physical and psychological symptoms of ketamine dependence among recreational users.

#### **Schedule 4 - Amendment**

KETAMINE – delete entry.

#### **Schedule 8 – New entry**

KETAMINE.

### **13.6            ARIPIPRAZOLE**

#### **PURPOSE**

The Committee considered the inclusion of aripiprazole in Appendix K of the SUSDP.

#### **BACKGROUND**

Aripiprazole is an atypical antipsychotic agent indicated for the treatment of schizophrenia. It is believed that the mechanism of its action is mediated through a combination of partial agonist activity at dopamine D2 receptors and serotonin 5-HT1A receptors and antagonist activity at 5-HT2A receptors.

The October 2003 NDPSC Meeting agreed to include aripiprazole in Schedule 4 of the SUSDP and to consider the possible inclusion in Appendix K at the next meeting. The February 2004 NDPSC meeting was advised of information drawn from open literature that aripiprazole has a high potential for causing sedation (Keck et al, Am J Psychiatry 2003; Potkin et al, Arch Gen Psychiatry 2003; Goodnick et al, Expert Opin Pharmacother 2002) and that there was a need to investigate this issue further. Members also noted the conflicting findings of a placebo-controlled 26-week study on schizophrenia patients



(Pigott et al, J Clin Psychiatry 2003), where aripiprazole was well tolerated, with no evidence of marked sedation. Subsequently, the Committee agreed to further investigate the need to include aripiprazole in Appendix K of the SUSDP and consider the matter again at a future meeting so expert advice on the issue could be sought.

## DISCUSSION

The Committee considered the expert advice received from XXXXXXXXXX. The XXXXXXXXXX advised that:

- The NDPSC request was considered by the XXXXXXXXXX at its 31 August 2004 meeting.
- While a review of the available literature was not undertaken, the current Product Information (PI) for aripiprazole listed somnolence as an adverse effect and quoted the pooled rates from four short-term placebo-controlled trials. The overall rates were quoted as 9.8% for aripiprazole and 6.4% for placebo, and consistent with those quoted by Marder et al. (11% vs 8%). The PI also stated that there was a dose-related effect, giving rates of 8.7% for the 15 mg dose, 7.5% for 20 mg, 15.3% for 30 mg and 7.7% for placebo. The information in the PI therefore appeared to accurately reflect the data from the pooled analysis of several published clinical trials.
- The PI for aripiprazole was compared with other antipsychotics, e.g. olanzapine, risperidone and quetiapine, in terms of the rate of incidence of somnolence/sedation. For olanzapine, sedation was listed as “infrequent” and “transient” and more common in children and adolescents. For quetiapine, the rate quoted was 3% compared with 0% for placebo and for haloperidol sedation was listed as an adverse effect with no further information.
- None of the PIs of the atypical antipsychotics or haloperidol examined carried a label warning statement even though for quetiapine and olanzapine at least, the quoted rates for sedation/somnolence were similar to those published for aripiprazole.
- From the point of view of clinical experience, the consensus view of the members of the Committee was that sedation did not appear to be a particular problem although it was noted that it could affect some patients, perhaps children and adolescents more than adults and that idiosyncratic reactions (prolonged sedation) had been reported (Davenport et al 2004).
- The Committee was of the opinion that “although sedation is an adverse effect of aripiprazole, the data suggest that it is not of such frequency or severity to justify a label statement. When compared to other atypical antipsychotics, none of which carries a warning, aripiprazole does not appear to be significantly worse and in fact may be less sedating than some. The current PI contained information which appeared to accurately inform the clinician of the potential for aripiprazole to cause sedation, without the need for a specific warning.”

The Chair noted that the XXXXXXXXXX did not provide advice on the general issue of the potential for atypical antipsychotics, as a class, to cause sedation.

Members noted that XXXXXXXXXX, the sponsor of aripiprazole, supported the proposal to include the substance in Appendix K of the SUSDP. In addition, the sponsor recommended that the warning statement “This medication may cause drowsiness. If affected do not drive a motor vehicle or operate machinery. Avoid alcohol.” be added to the dispensing label for aripiprazole.

The Committee discussed the following issues:

- The advice from XXXXXXXXXX highlighted an inconsistency in the way medicines with a potential to cause sedation was dealt with in the PI, Consumer Medicine Information (CMI), SUSDP Appendix K, and the Australian Pharmaceutical Formulary and Handbook (APF). As an example, it was noted that the PI for some atypical antipsychotics including haloperidol and olanzapine did not carry a sedation warning and yet these drugs were listed in Appendix K of the SUSDP.
- The Committee noted that the need to retain Appendix K, as well as other appendices in the SUSDP, was an issue that required resolution ideally before the new Trans-Tasman Therapeutic Agency commenced operation. Members advised that Appendix K was in effect in some jurisdictions and acknowledged that it was essential to send a consistent message through Appendix K, the PI and the CMI to doctors, pharmacists and consumers with respect to the potential for medicines to cause sedation. The Consumer representative advocated that labelling of the immediate container of dispensed medicines with a sedation warning would ensure that patients or their carers would have immediate access to this information.
- The Committee noted that the need to include a sedation warning in the PI or CMI is routinely assessed at product registration. To promote consistency and to assist the NDPSC in determining whether it is appropriate to list a medicine in Appendix K, it was agreed that the TGA be asked that specific recommendations on the sedation potential of medicines be included in product evaluation reports, ADEC and MEC minutes, and in the advice of Delegates. Furthermore, the Committee agreed that the evidence on which sedation warning statements are based should be clear and specifically addressed in the evaluation reports.

## **OUTCOME**

The NDPSC noted the expert advice from the XXXXXXXXXX that whilst sedation is an adverse effect of aripiprazole, the data suggests that it is not of such frequency or severity to justify a label warning statement.

[Item removed]

### **13.8            ROSUVASTATIN**

#### **PURPOSE**

The Committee considered the inclusion of rosuvastatin in Appendix D of the SUSDP.

#### **BACKGROUND**

Following the February 2004 ADEC meeting's approval of an application by XXXXXXXXXX to register XXXXXXXXXX, the June 2004 NDPSC meeting agreed to include the new medicine rosuvastatin in Schedule 4 of the SUSDP.

Rosuvastatin is a potent HMG-CoA reductase inhibitor (statin) and the June 2004 NDPSC meeting noted that other statins in this class carry a Pregnancy Category C in Australia. The meeting noted also that the Drugdex Drug Evaluation included a USFDA pregnancy Category X for rosuvastatin and pregnancy warnings in the Patient Instructions for XXXXXXXXXX.

The Committee requested that the Secretariat investigate the pregnancy category for all statins in this class and seek comment from ADEC.

#### **DISCUSSION**

The Committee noted advice received from XXXXXXXXXX that it did not have any specific input at this stage regarding the inclusion of rosuvastatin in Appendix D, but requested to be kept informed.

The Committee noted also that comment had not been received from ADEC.

#### **OUTCOME**

The Committee agreed to defer consideration to the February 2005 meeting pending advice from ADEC.

### **13.9            DICLOFENAC**

#### **PURPOSE**

The Committee received a submission from XXXXXXXXXX in relation to the outcome of the June 2004 meeting consideration of the scheduling of low dose diclofenac.

#### **BACKGROUND**

The June 2004 meeting did not agree with the proposal from XXXXXXXXXX to reschedule from Schedule 3 (S3) to S2 diclofenac in divided preparations for oral use

containing 12.5 mg or less per dosage unit in a pack containing 30 or less dosage units. The Committee was not convinced that rescheduling 12.5 mg diclofenac to S2 was appropriate at that time in the absence of an evaluation for OTC registration and in the absence of local post-marketing experience with the 12.5 mg oral dose formulation in Australia to establish the product's safety, efficacy and use pattern for the indications sought.

## DISCUSSION

XXXXXXXXXX participated in the discussion of this item via telephone.

The Committee noted a submission had been received from XXXXXXXXXX seeking reconsideration of the June 2004 NDPSC decision. XXXXXXXXXX expressed concern that the decision was inconsistent with the evidence submitted to the Committee and XXXXXXXXXX response to several points raised in the June 2004 Record of Reasons relating to diclofenac 12.5 mg was submitted for consideration. The submission also contained a tabulation of the worldwide registration status of diclofenac potassium 12.5 mg tablets (as at August 2004) and adverse events update for diclofenac-K 12.5 mg for the period 1 September 2000 to 30 June 2004.

The NDPSC was informed that the MEC Secretariat had requested additional data to allow finalisation of the registration evaluation report. Members asked that the MEC evaluation report be provided to the NDPSC when it becomes available.

## OUTCOME

The Committee noted the additional material submitted by the sponsor and agreed that the submission could not be considered as a new scheduling application at this meeting as it was received after the publication of the pre-October 2004 meeting gazette notice. Furthermore, the Committee indicated that it was open for the sponsor to reapply for scheduling consideration at a future NDPSC meeting provided the application is received by the Secretariat within the specified timeframe.

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

#### **14.1 SUSDP, PART 4**

[Item removed]

#### 14.1.2 NEOMYCIN, POLYMYXIN & BACITRACIN

##### PURPOSE

The Committee considered a proposal to reschedule XXXXXXXXXX from Schedule 4 (S4) to S3 with inclusion in Appendix H of neomycin, polymyxin and bacitracin combination.

##### BACKGROUND

XXXXXXX is a combined-antibiotic preparation, containing neomycin sulphate 5 mg/g, polymyxin B sulphate 5000 units/g, and bacitracin zinc 400 units/g. The proposed indication is for the treatment and prevention of infection in certain skin conditions including minor cuts, scrapes and burns through eradication of susceptible bacteria. The current approved indication for the product is for the eradication of susceptible organisms in dermatological conditions including primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia), secondarily infected dermatoses (eczema, Herpes simplex, seborrheic dermatitis), traumatic lesions, and lesions with bacterial infection.

The August 2001 Meeting considered an application by XXXXXXXXXX (subsequently renamed to XXXXXXXXXX following the merger between XXXXXXXXXX and XXXXXXXXXX) to reschedule XXXXXXXXXX from S4 to S3, with inclusion of the active ingredients in Appendix H. However, the rescheduling proposal was not supported at the time on the basis of advice received from the Expert Advisory Group on Antimicrobial Resistance (EAGAR) and documented evidence of neomycin resistance worldwide. Furthermore, the Committee was unable to assess the risks associated with antibiotic resistance and cross-resistance with respect to bacitracin, neomycin and polymyxin due to the lack of positive data or evidence at the time of consideration.

The EAGAR advised the August 2001 NDPSC meeting that neomycin should remain in S4 for all dosage levels and formulations except vaccines, which did not require scheduling. This advice was based on the potential for selection of cross-resistance to other aminoglycosides with the resulting loss of agents of medium/high importance in the treatment of human infections and co-selection of resistance in other classes of antibiotics.

The EAGAR in its assessment of bacitracin, in the context of its use as antibiotic and growth promotant in food-producing animals, advised the February 2003 meeting that scheduling bacitracin outside S4 would pose an unacceptable risk of promoting antimicrobial resistance.

##### DISCUSSION

XXXXXXX participated in the discussion of this item via telephone.

The Committee noted XXXXXXXXXX's submission seeking to reschedule its product, XXXXXXXXXX, from S4 to S3 comprised of two volumes. Volume 1 contained the original application considered in 2001 while volume 2 included a recent *in vitro* study which examined the potential for XXXXXXXXXX to develop resistance or cross-resistance. XXXXXXXXXX raised the following points in support of its application:

- Minor skin trauma is clearly disposed to self-medication. While many antiseptic products are available, there is still no appropriate antiseptic agent for use on the skin. Historical clinical use and more recent controlled clinical trials supported the efficacy of the product in preventing infections in certain skin conditions and minor trauma, which could be readily self-treated, and in enhancing wound healing.
- XXXXXXXXXX has a long history of safe use where it has been available for over 30 years in Australia as a prescription drug and for approximately 30 years as an OTC medication in the US. Sales of the product in Australia over 1998-2000 were approximately XXXXXXXXXX units and approximately XXXXXXXXXX units in the US for the same period.
- The active ingredients, i.e. neomycin sulphate, polymyxin B sulphate, and bacitracin zinc, had been found to be inappropriate for parenteral and oral use due to adverse effects thus reducing the possibility of resistance developing to valuable systemic antibiotics.
- From the significant and widespread topical use of these antibiotics, issues only emerged for neomycin. These issues were in regard to ototoxicity, allergic contact dermatitis and the possibility of the development of resistance. These issues are addressed below:
  - The issue of ototoxicity associated with neomycin was mainly reported in situations of high exposure, such as in wound irrigation. With the ointment presentation, despite the large number of units sold, there had been no reports of deafness in Australia and no medically confirmed reports of deafness in the US during its nearly 30 years of use.
  - Whilst dermal absorption did occur to a certain extent for all three actives, an equivalent to 40 tubes of XXXXXXXXXX is required for systemic toxicity to occur. The sponsor indicated that contact dermatitis could occur from use of XXXXXXXXXX but the prevalence of this side effect in the setting of self-medication of minor skin trauma was considered acceptable based on an incidence rate of 0.1-1% (Prystowsky *et al*, 1979 a and b; Leyden and Kligman, 1979). Furthermore, the submission had stated that “reviews of the issue have concluded that, as well as the prevalence being low enough to be considered acceptable, when allergic contact dermatitis does occur when used in this way, it is likely to be a mild reaction that will resolve on withdrawal of treatment.”
  - The issue of resistance development had been identified in closed hospital populations and had never been reported in the setting proposed. The risks associated with possible emergence of resistant micro-organisms from use of

XXXXXXXXXX were deemed to be low (Leyden & Sulzbeger, 1981; Eady *et al* 1982) to unlikely when used occasionally for treating minor skin trauma. The use of a triple antibiotic, as opposed to the single active ingredient, is less unlikely to result in the development of resistance since the complimentary and overlapping antibacterial spectra ensures the elimination of any mutant organisms (J. Langford 1995). Macdonald and Beck (1983) also concluded that use of neomycin topically in modest amounts for short periods (up to a week) should not result in a complication such as resistance. The actives are no longer used systemically which further reduces the potential for resistance occurring with these agents.

- The public would benefit by making XXXXXXXXXX more readily available to self-treat skin conditions and prevent infection in minor skin trauma. No significant safety issues had been identified for topical application of the product for short periods to mildly inflamed but infected skin (Macdonald and Beck, 1983), on an occasional basis.
- XXXXXXXXXX or its equivalent is available as follows:
  - Australia – Prescription
  - New Zealand – Prescription
  - USA – OTC
  - Canada – Prescription Only; XXXXXXXXXX (bacitracin & polymyxin B) is OTC
  - Europe – not marketed in most countries
- Education programs would be focussed on community pharmacists. This will involve one-on-one professional detailing/training regarding:
  - general principles of wound care and infection;
  - appropriate use of topical antibiotics;
  - basic advice required to be given to patients;
  - when patients need to be referred to a doctor or clinic;
  - how to deal with reports of possible adverse events;
  - supportive services provided by the company, e.g. medical information inquiry line; and
  - printed and video training material will also be distributed to pharmacists for reference purposes, as well as relevant literature publications.
- Inclusion of the combination active ingredients in Appendix H of the SUSDP was also sought.

Members noted that the evaluator of the sponsor's submission considered the *in vitro* study presented to be flawed. The evaluator indicated that the study design did not allow for any conclusion to be made on the question of resistance selection potential. In particular, a comparison of resistance rates in areas of high (OTC) and low (prescription

only) use could not be drawn and the evaluator considered this an important question to answer. The evaluator stated that “The data required (prevalence of gentamicin resistance in all *Staphylococcus aureus*) are available through the Australian Group on Antimicrobial Resistance and re analysis using comparable methods including the use of the same breakpoints is possible. Unless there is a mechanism whereby the sponsor can resubmit the reanalysed data there is no reason to alter the decision made when this was last considered at the NDPSC. XXXXXXXXXX should remain in Schedule 4 of the SUSDP”. Accordingly, the evaluator did not support the sponsor’s proposal to include the combination ingredients in Appendix H.

The EAGAR had been asked to comment and peer review the evaluation report on XXXXXXXXXX’s rescheduling application to the October 2004 meeting. The Committee noted EAGAR’s opinion that there was no new evidence to justify any change to the scheduling of XXXXXXXXXX and confirmed its previous advice that this product should remain in Schedule 4.

A member pointed out that EAGAR’s advice to the NDPSC in 2001, highlighted that Australia’s guidelines for the use of antibiotics did not endorse the use of topical neomycin combinations for either the prevention or the treatment of skin infections. EAGAR pointed out that the preferred prophylaxis for burns is silver sulfadiazine 1% plus chlorhexidine 0.2% cream. The member further added that the large pack size containing 15g of the preparation could lend itself to indiscriminate and excessive use of the product for minor cuts and burns which could consequently accelerate the rate of cross-resistance development.

The Committee noted the pre-meeting submission received from XXXXXXXXXX advising the NDPSC that it marketed an otic preparation containing neomycin and bacitracin. The company opposed the OTC availability of any topical neomycin products on the following grounds:

- There are diagnostic issues associated with the use of XXXXXXXXXX’s product and all forms of neomycin products. The company considered it inappropriate that such products should be made available without a medical examination or assessment.
- Martindale, “Complete Drug Reference 2003” Pharmaceutical Press states “Neomycin has particularly potent nephrotoxic and ototoxic properties and so is generally no longer given parenterally. However, sufficient may be absorbed following administration by other routes (e.g. oral administration, instillation into cavities or open wounds, or topical administration to damaged skin), to produce irreversible partial or total deafness. The effect is dose-related and is enhanced by renal impairment.”
- Product information for several topical neomycin products currently available in Australia contained similar warnings concerning the danger of misuse or excessive use of neomycin. In addition, the product had the potential to cause irreversible hearing loss if used when the tympanic membrane is perforated hence in this use medical diagnosis is required.



XXXXXXXXXX also provided comment on XXXXXXXXXX's proposal supporting the recommendation of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) that ALL antibiotics for use in humans and animals (and fish) should be S4. XXXXXXXXXX indicated that widespread use of neomycin, polymyxin and bacitracin, whether topical or oral, would select resistant strains and increase the rate of selection of antibiotic resistant organisms.

A member advised that XXXXXXXXXX was still a prescription only medicine in NZ and indicated that it was unlikely to be allowed for use outside the supervision of a medical practitioner due to concerns over cross-resistance to important antibiotics used in humans.

## **OUTCOME**

Based on the available information and advice received, the Committee confirmed that the current scheduling of neomycin, bacitracin and polymyxin remained appropriate. Members were of the view that the proposed indication for XXXXXXXXXX as S3 medicine had the potential to encourage excessive and unnecessary use of the product and increase the potential rate of resistance development.

### **14.1.3 OSELTAMIVIR**

#### **PURPOSE**

The Committee considered a proposal to reschedule oseltamivir from Schedule 4 (S4) to S3.

#### **BACKGROUND**

Oseltamivir is a pro-drug of the active metabolite oseltamivir carboxylate. The active metabolite selectively inhibits influenza virus neuraminidase enzymes which are essential for the replication of both influenza A and B viruses. XXXXXXXXXX is not a substrate for or inhibitor of the cytochrome P450 isoforms.

The November 2000 NDPSC Meeting agreed to include oseltamivir in S4 of the SUSDP following consideration by the ADEC of an application to register XXXXXXXXXX, containing 75 mg of oseltamivir phosphate, for the treatment of infections due to Influenza A and B viruses in adults and children aged twelve years and older. XXXXXXXXXX was launched in Australia as S4 medicine in January 2001 and was approved for the treatment of infections due to influenza A and B viruses in adults and children aged one year and older.

#### **DISCUSSION**

XXXXXXXXXX participated in the discussion of this item via telephone.

The Committee noted XXXXXXXXXX's submission highlighting the following points in support of its application:

- XXXXXXXXXX has an excellent safety profile with very few side effects. In clinical trials, the most frequently reported adverse events were nausea and vomiting. These symptoms were transient and typically occurred with the first dose. A pharmacist could advise that these side effects may be reduced by taking XXXXXXXXXX with food. Post marketing experience had only led to the inclusion of very few additional adverse events in the product information, all of which occurred rarely or very rarely.
- Influenza symptoms are easily recognised by the patient with assistance from a pharmacist and are amenable to short-term treatment which do not require medical management or direct supervision by a doctor.
- Oseltamivir has low abuse potential. There is no preclinical evidence to show that the active metabolite could affect the central nervous system (CNS) and any CNS effects due to oseltamivir itself occurs at extremely high plasma concentrations, approximately 4000 fold higher than average human peak plasma levels. Seven Periodic Safety Update Reports (PSUR) had been completed since October 1999 and there had been no reports of abuse, misuse, dependency or withdrawal association with XXXXXXXXXX treatment.
- XXXXXXXXXX has a wide therapeutic window and minimal drug to drug interactions. To date, there had been no reported cases of overdose and doses up to 7.5 times the recommended daily dose taken for 7 days had been well tolerated. It would be most likely that if inappropriate use of XXXXXXXXXX would occur it would be for patients that have a "common cold" rather than influenza or if patients took the product outside the 48-hour window of effectiveness. In both situations there would be no adverse consequences for the patient. XXXXXXXXXX was working closely with professional bodies to develop protocols for the treatment of influenza to ensure that the pharmacist would have all the appropriate information to allow a correct assessment of the disease state when a patient presented with influenza-like symptoms. When influenza is known to be circulating in the community, clinical assessment of influenza is highly accurate with the aid of a simple case definition, i.e. a patient must have fever at  $>38^{\circ}\text{C}$ , fatigue and cough. The case definition would be proposed for incorporation into pharmacy protocols for XXXXXXXXXX in S3. The submission included details of Pharmacy education (training and protocols) and support for pharmacists in supplying XXXXXXXXXX as an S3 medicine.
- Given that the proposed indication for XXXXXXXXXX in S3 excluded children aged one to 13 years, the risk of masking a serious disease or compromising medical management in the most vulnerable group would be limited. During clinical trials for prophylaxis, patients including elderly subjects received XXXXXXXXXX at the recommended dose of 75 mg once daily for six weeks continuously and no additional safety or tolerability issues were evident. The only contra-indication to XXXXXXXXXX is hypersensitivity to any components of the product.

- Monitoring of resistance to the neuraminidase inhibitor (NI) class of drugs, Neuraminidase Inhibitor Susceptibility Network (NISN), was set up in 1999 to oversee global surveillance. To date, data presented by the NISN group and a number of other studies including surveillance from Australia, had shown that mutations conferring resistance to NIs occurred very rarely and were typically less virulent than wild-type viruses and they spread less easily. Ferguson *et al* recently predicted the potential for drug-resistant influenza to spread in the community due to NI therapy using a mathematical model of influenza transmission. The model was developed using current epidemiological, clinical and experimental data. Whilst acknowledging the limitations of modelling due to the various assumptions required to capture the dynamics of influenza transmission, the model clearly showed that even with very high levels of drug usage there was no significant transmission of neuraminidase resistant virus. Furthermore, increasing access to XXXXXXXXXX would reduce the incidence of antibiotic-resistant micro-organisms from inappropriate prescribing of antibiotics.
- Timing and access to XXXXXXXXXX treatment is of critical importance. Obtaining XXXXXXXXXX via prescription is a barrier to access. The Influenza Specialist Group (ISG) estimated that only about 12% of Australians under the age of 65 obtained vaccination each year. Given the excellent profile of the drug and in terms of disease management and prevention of further complications from influenza, the pharmacist is in the best position to offer appropriate advice and provide immediate treatment.
- From a public health perspective S3 access to the treatment with XXXXXXXXXX offers numerous potential public health benefits including a reduction in the number of deaths attributed to influenza and pneumonia, a reduction in the spread of influenza infection in the community and a reduction in the overall economic cost and burden to society.

Members also noted that the sponsor raised the following potential health benefits from the inclusion of oseltamivir in Appendix H of the SUSDP. The sponsor had claimed that advertising oseltamivir would promote:

- awareness of the difference between “cold” and “flu” and that treatment for influenza needs to commence no later than 48 hours after the onset of the initial symptoms of infection;
- awareness of an effective and safe treatment option for influenza available upon advice from a pharmacist; and
- awareness that treatment will prevent further spread of disease in the community.

The Committee noted that XXXXXXXXXX submitted additional data for consideration of the NDPSC in the form of an expert commentary by XXXXXXXXXX on the non-prescription use of XXXXXXXXXX for the treatment of influenza. XXXXXXXXXX supported the OTC availability of XXXXXXXXXX and highlighted the following points:

- The diagnosis of influenza is accurate and relatively easy during an epidemic or outbreak, and the pharmacist is well placed and well trained to diagnose the disease. Influenza epidemic occurs in the Northern and Southern hemispheres during a very restricted period in the winter season only and extremely small quantities of XXXXXXXXXX would be utilised. Diagnosis of influenza outside the epidemic period is more difficult.
- It is appropriate to focus on the 30% of patients who are misdiagnosed because their symptoms are caused by another virus, such as RSV or a bacterial infection. Compared to bacterial infections, the microbiological situation with influenza is very different. Thus there are no carriers of influenza, whereas the symptomless carrier rate of *St. Pneumonia*, for example, could be significant. On this basis, there would be no opportunity for drug resistant influenza viruses to be selected in the “misdiagnosed” group, even if they had access to XXXXXXXXXX. In contrast, with antibiotics there are always opportunities to select drug resistant bacteria because they would be present in otherwise healthy persons as well as in patients with illness. The influenza burden of an individual is likely to be around  $10^7$  viruses, which is significantly different from bacteria by 18 orders of magnitude, thus, the opportunities for emergence of drug resistant influenza viruses are very much reduced compared to bacteria.
- At least two international groups had been established to monitor for any emergence of drug resistant influenza viruses and to characterise these viruses. To date, less than twenty NI resistant influenza viruses had been detected worldwide despite quite extensive use of XXXXXXXXXX in Japan, Australia, USA and certain European countries. A small group of NI resistant viruses was detected in influenza infected children in Japan (Kiso *et al*, 2004; Moscona, 2004). However, the patients had not been treated according to international guidelines and, for example, the children were treated with less than the recommended dose of XXXXXXXXXX. WHO had, in the face of new deaths of children from chicken influenza (H5N1), argued that XXXXXXXXXX was at the center of preventative and therapeutic intervention for influenza. Early studies (reviewed by Field & Goldthorpe, 1980) demonstrated that although drug resistant viruses could be detected, albeit rarely, such viruses were less pathogenic than drug sensitive viruses in animal model infections. This indicated that drug resistant viruses could have a grown disadvantage and would be always overtaken by fully replicative drug sensitive viruses (reviewed by Field & Goldthorpe, 1980). Similarly, studies of the NI drugs both in the clinic and the laboratory had shown that XXXXXXXXXX resistant influenza A (H1N1, H3N2) and B viruses emerged only very infrequently. These influenza viruses had been shown to be less virulent in animal models and had less ability to spread from animal to animal (Ives *et al*, 2002; Herlacher *et al*, 2002). Therefore, it was deduced that, like the acyclovir resistant herpes viruses, the drug resistant influenza viruses would be crippled and would be continually overtaken in the community by fully competent and drug sensitive influenza viruses. The drug resistant viruses have no growth advantage in the community and are unlikely to spread.

- Timely access to the drug is essential for the treatment of infected persons and this is more readily achieved if a pharmacist supplies the drug rather than a GP. The potential public health benefit from reduced mortality and primary care cases would be significant with OTC availability of XXXXXXXXXX. Using clinical consultation with GPs as a proxy for severity of illness, from the data collected in the national sentinel physicians networks in the UK and The Netherlands over the last 10 years, the estimates of consultation were approximately 3% of the population consulting with influenza, although a number of studies indicated that the attack rates in the population during an influenza epidemic ranged from 5-15%.
- Whilst Influenza vaccines will continue to be the cornerstone of influenza management in the elderly and ‘at risk’ groups, it is not 100% protective against the disease and certainly not against infection. Therefore, each year a number of previously vaccinated ‘at risk’ persons will become infected with influenza and are vulnerable to severe respiratory complications. Also, there exists a cohort of perhaps 30-40% of the ‘at risk’ group who do not receive the vaccine. These persons would be excellent candidates for chemotherapy with the new NIs, such as XXXXXXXXXX. In the UK, NIs are particularly targeted to the ‘at risk’ group.

The Committee noted the information package submitted by XXXXXXXXXX providing the details of how it planned to deliver to pharmacies the education, training and practise support materials for XXXXXXXXXX in the S3 setting including the timelines for the delivery of the information, if XXXXXXXXXX was rescheduled in S3.

The evaluator of the sponsor’s submission did not support the rescheduling of oseltamivir to Schedule 3 at that time. The evaluation report raised the following key points:

- Oseltamivir (XXXXXXXXXX) is an anti-viral agent of the neuraminidase class that has demonstrated efficacy in the treatment and prevention of influenza provided therapy is commenced within 36-48 hours of the onset of symptoms. While the sponsor asserted that the clinical diagnosis of influenza was reliable, the data and clinical experience did not support this contention. Furthermore, there is the potential to misdiagnose bacterial pneumonia and potentially delay appropriate therapy without thorough medical assessment.
- Point-of-care tests are available for the diagnosis of influenza but are not incorporated in the algorithms suggested for distribution under Schedule 3. Further assessment of the appropriateness of rescheduling may be undertaken on the basis of the availability and incorporation of point-of-care testing into the distribution algorithm.
- The potential for the development and spread of resistance to NIs has been explored but data to date is preliminary and insufficient to provide reassurance that widespread use of these agents would not result in increasing prevalence of such resistance. Further evaluation of the development, spread and prevalence of resistance to NIs in countries where Oseltamivir (XXXXXXXXXX) is available, and in particular in settings where use is widespread, should be undertaken.

- Accordingly, the evaluator did not support the inclusion in Appendix H of the SUSDP, as S3 was not recommended. However, the evaluator indicated that should the NDPSC decide to accept the submission for rescheduling of oseltamivir to Schedule 3 it was recommended that oseltamivir be added accordingly to Appendix H.

Members noted that EAGAR had agreed to provide advice on oseltamivir and supported the recommendations in the evaluation report, ie the substance remain in S4.

XXXXXXXXXX provided comment to the NDPSC supporting the rescheduling proposal to make the product more readily accessible, i.e. for use within 48 hours after onset of initial symptoms. XXXXXXXXXXXX had stated that “there are near patient tests available which could be undertaken before purchase which would only be permitted if the test was positive and could therefore be consideration to make this product available as S2 with the positive test proviso.”

The Committee noted that public submissions (\* late submissions) had been received from XXXXXXXXXXXX, XXXXXXXXXXXX, XXXXXXXXXXXX, XXXXXXXXXXXX, XXXXXXXXXXXX\*, XXXXXXXXXXXX, XXXXXXXXXXXX and XXXXXXXXXXXX \*. All the submissions except XXXXXXXXXXXX supported the OTC availability of XXXXXXXXXXXX. The following issues were raised:

- Oseltamivir is safe and efficacious for the prevention and treatment of influenza (A and B virus) in adults and adolescents 13 years and older.
- Oseltamivir is well tolerated and has a low incidence of adverse events (mostly mild or moderate) and the potential for interactions with other drugs is limited to those arising from competitive inhibition of excretion by the renal tubular epithelial cell anionic transporter. The most common and the only clinically important side effect is mild gastrointestinal upset; mainly nausea and vomiting. However, it had been shown that the incidence of nausea had been further reduced when the first dose was taken with food (Aoki FY, M.M, Paggiaro P *et.al*, 2003).
- Professional pharmacy organisations were working with the sponsor to assist in the development and delivery of practice tools and guidelines for the pharmacy profession in a timely manner and ensure that the professional advice and support provided to consumers would be of the highest standard.
- The consumer is able to identify the symptoms of cold and flu and pharmacists are competent to make a differential assessment between influenza, allergies, bacterial sore throat and viral upper respiratory tract infections, as well as make referrals to a medical practitioner. Experience had shown that the use of an appropriate case definition facilitated an accurate diagnosis in at least 60-70% of cases.
- Increasing the availability of oseltamivir for the treatment of influenza facilitates timely access and enhances the efficacy of this medicine (Aoki, Macleod, Paggiaro-*et-al*: Journal of Antimicrobial Chemotherapy (2003) 51, 123-129). Access to a medical practitioner within the window of opportunity is an issue for consumers,

particularly for the elderly. In addition, infected individuals left in a general practitioner's waiting room are likely to spread influenza to other patients whereas this is less likely in a pharmacy setting. The current arrangements do not promote widespread use of anti-viral drugs but are associated with morbidity including pneumonia, and even death, because of the difficulty in accessing prescription only anti-influenza drugs.

- Whilst the Australian Society for Geriatric Medicine had recently revised its vaccination guidelines for older people to clearly state that anti-viral drugs should not replace a yearly influenza vaccination, vaccination does not provide complete protection either. This could be due to a poor match of the vaccine strain or a poor immune response. Estimates of protective efficacy vary from 70-90% in healthy individuals, 65 years old [McKimm-Breschkin, J. (2002)] and influenza vaccine is only 40-60% effective in elderly patients, especially nursing home residents and patients with immunosuppression [Stiver, G. (2003)]. In the event of a pandemic, vaccines are not effective at the point of outbreak.
- The nationally endorsed case definition for influenza should be used as a checklist by a pharmacist and the drug to be offered within 48 hours after the onset of symptoms to those patients testing positive, based on the case definition, provided it is during an epidemic activity in the community. Use in any other situation should be through prescription only. It is important that patients are fully aware that oseltamivir may not benefit them, even if they meet the case definition criteria, as there is 20-80% chance that they do not have influenza virus infection. This is unlikely to be any better if the medication is prescribed, as doctors have the same difficulty in clinically diagnosing influenza. Patients who meet the NHMRC criteria for high risk of severe or complicated influenza should still be encouraged to see a doctor, whether or not they are treated with oseltamivir.
- Whilst there were some concerns about the potential for resistance to develop with widespread use of anti-viral drugs, the presence of a resistant organism in an individual does not indicate that the organism would be spread as the virulence and infectivity of the organism is likely to be reduced by the anti-viral drug. The data so far indicated that the resistant viruses were uncommon, had not been transmitted to people, did not cause ongoing illness, and disappeared after cessation of treatment. If approval was given for S3, it would be essential that monitoring of resistance continued and if there was any evidence of increasing resistance in the community, the scheduling of oseltamivir should be reviewed. The current data and experience with other antivirals (aciclovir, valaciclovir and famciclovir) does not suggest that this is likely to be a problem. To limit this likelihood it is important that patients take the full course.
- In the S3 setting, it would be necessary for pharmacists to advise a patient to seek medical attention if there were no signs of improvement within 24 hours of starting the course of medication. Such safeguards should be built into any pharmacy treatment protocols.

- The XXXXXXXXXX and XXXXXXXXXX supported an Appendix H listing for oseltamivir. XXXXXXXXXX stated that the need for early treatment and the low risk profile of the medicine made it appropriate and in the public interest to be advertised.
- The XXXXXXXXXX highlighted that the product information for oseltamivir identified a range of precautions, possible allergic reactions, adverse effects, and contraindications, all of which would necessitate medical advice before taking this medicine, and certainly if these occurred. These included phlegm producing cough or wheezing, diarrhoea, nausea, vomiting, abdominal or stomach pain, bloody nose or unexplained nosebleeds (occurs mainly in children), burning, dry or itching eyes, redness, pain, swelling of eye or eyelid, or excessive tearing (occurs mainly in children), cough, dizziness, ear disorder (occurs mainly in children), fatigue, headache, and trouble in sleeping. XXXXXXXXXX pointed out that oseltamivir had not been studied in pregnant women, that it was not known whether the drug passes into human breast milk and that oseltamivir had not been tested in children younger than 1 year of age. XXXXXXXXXX indicated that medical advice would be required for use in children under 1 year and in individuals with medical problems, e.g. kidney disease, heart disease, illnesses caused by viruses other than Influenza Type A or B, liver disease and lung disease.

The Committee noted that the XXXXXXXXXX, XXXXXXXXXX, wrote to the XXXXXXXXXX seeking a deferral of any decision at the next NDPSC meeting regarding oseltamivir to allow input from the National Influenza Pandemic Action Committee (NIPAC). Whilst XXXXXXXXXX had acknowledged that there may be advantages in having influenza anti-virals available over-the-counter, i.e. patients may be able to commence the medication earlier and possible reduction in the overall virus circulating in the community, XXXXXXXXXX alluded to the following issues as requiring consideration:

- The likely impact during a pandemic of rapid depletion of antiviral stocks in pharmacies. This would have the potential of limiting the ability of the States and Territories, the Australian Government and industry working together to effectively use circulating stores of anti-virals. [sentence removed]
- The potential for considerable wastage through inappropriate use;
- The potential for resistance to develop; and
- The potential reduction of vaccine use in the inter-pandemic period.

Members noted that oseltamivir is a relatively new drug, with under 4 years clinical experience in Australia at prescription level. In spite of the information presented, some members still expressed a concern that there was a significant potential for XXXXXXXXXX to be misused by consumers for the treatment of the common cold, which most people refer to as the “flu”.

A member noted that the sponsor had presented an analysis of UK data on oseltamivir in support of its application for S3 availability of XXXXXXXXXX. It was pointed out that in



the UK, there had been limited experience with the supply of oseltamivir without the prescription of a doctor. Specially trained pharmacists supply the drug to “at risk” groups, as defined by the National Institute of Clinical Excellence (NICE) guidelines. It was indicated that supply via this mechanism was reimbursed by the National Health Service and was only activated if the level of influenza circulating in the local community was determined to have reached a critical level. The member noted that these schemes were called Patient Group Direction (PDG) schemes and of the 98 PGDs set up in the UK, only 5 were activated during the 2003/2004 influenza season. Members agreed that further information was necessary to gain a better insight into how the UK data could be used as a basis for the rescheduling of oseltamivir, given that the mechanism through which the drug was supplied in the UK outside a doctor’s prescription was not comparable to an Australian S3 availability.

Overall, the Committee considered the data available inadequate in providing a reassurance that widening the availability of oseltamivir for the treatment of influenza to S3 would not facilitate the spread of resistance to NI class of drugs. It was recognised that a conservative approach was integral to the overall management of the resistance issue, as reversing an increasing trend of resistance incidence rate may not always be possible. Furthermore, the Committee considered it helpful to have an optimised point-of-care test incorporated into the supply algorithm for XXXXXXXXX if pharmacists were to supply this product as an S3 medicine.

## **OUTCOME**

The Committee agreed to defer making a decision on the proposal to reschedule oseltamivir for the treatment of influenza to the February 2005 meeting to allow input by the National Influenza Pandemic Action Committee (NIPAC). Members considered it valuable to the Committee’s consideration if advice was received from authorities that deal with communicable diseases to gain an understanding of the implications an S3 availability of oseltamivir for the treatment of influenza would have on the national strategies for managing influenza epidemics or pandemics.

### **14.1.4 SILICONES**

#### **PURPOSE**

The Committee considered a proposal to include all silicones in Appendix C of the SUSDP except preparations for intraocular use.

#### **BACKGROUND**

The August 1993 meeting agreed to include injectable forms of collagen and silicone for human use in Schedule 4 of the SUSDP while injectable silicones for tissue augmentation was included in Appendix C. This matter arose for consideration at the request of NCCTG due to inappropriate use and heavy promotion of injectable collagen and silicone to women in beauty salons. The NCCTG was of the view that these products should only

be administered by qualified medical practitioners within a clinical setting and that scheduling would ensure an appropriate level of control. Some of the problems associated with silicones highlighted at the August 1993 meeting included the following:

- anecdotal reports of unqualified persons injecting silicone oil;
- problem reports from women who had been treated by medical practitioners;
- industrial grade silicone oil being purchased from non-medical sources and used in clinics; and
- the on-going need for limited availability of injectable silicones.

## DISCUSSION

The Committee noted a submission from XXXXXXXXXX proposing to include all silicones except those for intraocular use in Appendix C of the SUSDP. The following background information was provided by XXXXXXXXXX:

- A case had recently occurred in Victoria where a cosmetic surgeon had been using liquid silicone on patients as a filler for acne scarring and other skin imperfections. The XXXXXXXXXX had been given information that the silicone used was in small containers which the doctor had claimed were obtained from New York. The doctor stated that the surgery had the means to sterilise the product before use.
- The doctor stated that legal opinion had been obtained which advised that the usage of the product fell within S4 conditions and that tissue augmentation was not carried out in the surgery.
- A search of the Internet suggested that there were no legitimate uses for silicone injection into the skin and the usage for injection was banned by the FDA and Canadian authorities.
- The XXXXXXXXXX was most concerned at the activities of this doctor and the fact that possibly other doctors may be carrying out similar procedures. The XXXXXXXXXX subsequently requested that the scheduling be reconsidered to prohibit the use of silicone for injection.

The Committee noted the advice from the Medical Devices Assessment (MDA) Section stating that amending the SUSDP to include in Appendix C all silicone preparations for injection into the skin was not expected to have an impact on approved medical devices. DSEB also advised that the removal of the S4 entry for silicones was unlikely to have an impact on any prescription product. Furthermore, the Committee was advised that there was no expected impact on veterinary products.

Members noted the no public submissions were received following gazettal of the intent to consider the scheduling of silicones in relation to the proposal to include all injectable preparations in Appendix C of the SUSDP.

**DECISION 2004/42 – 21**

The Committee agreed that it would be appropriate to include in Appendix C of the SUSDP all preparations containing silicones for injection or implantation into the skin, on the grounds of public health and safety. Members also noted that there were existing preparations containing silicone for use in intraocular surgery which remained appropriate for inclusion in S4.

**Schedule 4 – Amendment**

SILICONES – amend entry to read:

SILICONES for intra-ocular use.

**Appendix C – Amendment**

SILICONES – amend entry to read:

SILICONES for injection or implantation **except** when included in Schedule 4.

**14.2 SUSDP, PART 5**

**14.2.1 APPENDIX H**

No items were considered.

[Items removed]

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

**15.1 NEW SUBSTANCES**

**15.1.1 DISODIUM GADOXETATE**

**PURPOSE**

The Committee considered the scheduling of disodium gadoxetate.

## BACKGROUND

Gadoxetate (gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid, disodium salt) is a new hepatobiliary magnetic resonance imaging contrast agent based on the extracellular fluid marker gadopentetate [gadolinium-diethylenetriamine-pentaacetic acid (Magnevist)].

The April 2004 ADEC Meeting recommended the approval of an application by XXXXXXXXXX to register XXXXXXXXXX containing the new medicine disodium gadoxetate 181.43 mg/mL (0.25 mol/L) in glass vials and pre-filled syringes for use in adults for the enhancement of magnetic resonance imaging (MRI) of focal lesions of the liver.

ADEC also recommended that approval be subject to the finalisation of the Product Information to the satisfaction of the TGA.

## DISCUSSION

The Committee noted the minutes of the April 2004 ADEC Meeting and that gadoxetate is not a classified medicine in New Zealand.

The Committee noted that disodium gadoxetate, when used for the enhancement of MRI, would be exempt under the SUSDP Appendix A entry “*ENHANCING AGENTS for use in ultrasonic and magnetic resonance imaging*”.

## OUTCOME

The Committee confirmed that disodium gadoxetate, when used for the enhancement of MRI, is exempt from the requirements of scheduling through the SUSDP Appendix A entry ‘*ENHANCING AGENTS for use in ultrasonic and magnetic resonance imaging*’.

### 15.1.2 FOSAMPRENAVIR

## PURPOSE

The Committee considered the scheduling of fosamprenavir.

## BACKGROUND

Fosamprenavir is a prodrug of amprenavir, which is a protease inhibitor with antiviral activity against HIV. Fosamprenavir is used with other antiretrovirals for combination therapy of HIV infection

The April 2004 ADEC Meeting recommended the approval of an application by XXXXXXXXXX to register XXXXXXXXXX containing the new medicine fosamprenavir calcium, presented as 700 mg tablets and 50 mg/mL suspension for use in combination

with low dose ritonavir, for the treatment of Human Immunodeficiency Virus (HIV) infection in adults in combination with other antiretrovirals. [sentence removed]

ADEC also recommended that approval be subject to the finalisation of the Product Information to the satisfaction of TGA.

## **DISCUSSION**

The Committee noted the Minutes of the April 2004 ADEC Meeting [words removed]. However, ADEC agreed that [words removed] there was a clinical need for alternatives because resistance and adherence resulted in least resistance to virus.

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

## **DECISION 2004/42 – 22**

The Committee agreed to include fosamprenavir in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitates appropriate medical diagnosis and the safe use of the medicine requires patient management and monitoring by a medical professional.

### **Schedule 4 – New entry**

FOSAMPRENAVIR.

#### **15.1.3 LUMIRACOXIB**

### **PURPOSE**

The Committee considered the scheduling of lumiracoxib.

### **BACKGROUND**

Lumiracoxib is a selective cyclo-oxygenase-2 (COX-2) inhibitor - non-steroidal anti-inflammatory (NSAID) drug.

The April 2004 ADEC Meeting recommended the approval of an application by XXXXXXXXXX to register XXXXXXXXXX containing the new medicine lumiracoxib 200 mg and 400 mg tablets for use in:

- the symptomatic treatment of osteoarthritis
- the treatment of primary dysmenorrhoea in adults
- treatment of acute pain (as a once daily dosage of 400 mg for a maximum period of 5 days).

ADEC also recommended that approval be subject to the finalisation of the Product Information to the satisfaction of the TGA

## **DISCUSSION**

The Committee noted the Minutes of the April 2004 ADEC Meeting which reported that pain studies showed lumiracoxib to be efficacious for the treatment of osteoarthritis, dental and orthopaedic surgical acute pain and dysmenorrhoea pain. [sentence removed]

The Committee noted the approved PI for XXXXXXXXXX and that there were no unexpected safety concerns.

The Committee also noted that lumiracoxib is classified as a prescription medicine in New Zealand.

## **DECISION 2004/42 – 23**

The Committee agreed to include lumiracoxib in Schedule 4 of the SUSDP on the grounds that:

- the condition being treated necessitates appropriate medical diagnosis;
- the safe use of the medicine requires patient management and monitoring by a medical professional; and
- to harmonise scheduling with New Zealand.

### **Schedule 4 – New entry**

LUMIRACOXIB.

#### **15.1.4 CARBETOCIN**

### **PURPOSE**

The Committee considered the scheduling of carbetocin.

### **BACKGROUND**

Carbetocin is a synthetic analogue of oxytocin reported to have a longer duration of action.

The April 2004 ADEC Meeting recommended the approval of an application by XXXXXXXXXX to register XXXXXXXXXX containing the new medicine carbetocin 100 µg/mL Solution for Injection in ampoules for use for the prevention of uterine atony and

excessive bleeding in high risk patients following delivery of the infant by elective caesarian section under epidural or spinal anaesthesia.

ADEC also recommended that approval be subject to the finalisation of the Product Information to the satisfaction of the TGA.

## **DISCUSSION**

The Committee noted the Minutes of the April 2004 ADEC Meeting, the approved PI for XXXXXXXXXX and that carbetocin is classified as a prescription medicine in New Zealand.

## **DECISION 2004/42 – 24**

The Committee agreed to include carbetocin in Schedule 4 of the SUSDP on the grounds that:

- the condition being treated necessitates appropriate medical diagnosis;
- the safe use of the medicine requires patient management and monitoring by a medical professional; and
- to harmonise scheduling with New Zealand.

## **Schedule 4 – New entry**

CARBETOCIN.

### **15.1.5 PEMETREXED**

## **PURPOSE**

The Committee considered the scheduling of pemetrexed.

## **BACKGROUND**

Pemetrexed is primarily a thymidylate synthase inhibitor like raltitrexed, but it also inhibits other folate-dependent enzymes involved in purine synthesis.

The June 2004 ADEC Meeting recommended the approval of an application submitted by XXXXXXXXXX to register XXXXXXXXXX, containing the new medicine pemetrexed disodium 500 mg per vial for the following indications:

- for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin; and

- for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC), after prior platinum based therapy.

ADEC also recommended that approval be subject to the finalisation of the Product Information to the satisfaction of the TGA.

## **DISCUSSION**

The Committee noted that the June 2004 ADEC Meeting had agreed [words removed] had been demonstrated with the combination of pemetrexed and cisplatin in the treatment of malignant pleural mesothelioma and efficacy appeared comparable to docetaxel in the treatment of NSCLC.

The Committee noted the approved PI, which advises that XXXXXXXXXX has a Pregnancy Category D and should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. The Committee confirmed its long-standing policy of not including anti-cancer agents in Appendix D on the basis that their mode of action restricted use to medical specialists.

The Committee noted that pemetrexed is classified as a prescription medicine in New Zealand.

## **DECISION 2004/42 – 25**

The Committee agreed to include pemetrexed in Schedule 4 of the SUSDP on the grounds that:

- the condition being treated necessitates appropriate medical diagnosis;
- the safe use of the medicine requires patient management and monitoring by a medical professional;
- and to harmonise scheduling with New Zealand.

## **Schedule 4 – New entry**

PEMETREXED.

### **15.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)**

#### **15.2.1 KETOTIFEN**

## **DISCUSSION**

The Committee noted that the April 2004 ADEC Meeting recommended the approval of an application by XXXXXXXXXX to register XXXXXXXXXX, containing the new



medicine ketotifen (present as ketotifen hydrogen fumarate) 250 µg/mL ophthalmic solution in bottles for use in the symptomatic short term treatment of seasonal allergic conjunctivitis in adults and children 3 years or older.

## OUTCOME

The Committee noted the decision of the November 1998 NDPSC Meeting to include ketotifen in Schedule 4 of the SUSDP as a result of consideration of scheduling proposals arising from the July 1998 TTHWP Meeting.

[Item removed]

## 16. OTHER MATTERS FOR CONSIDERATION

[Item removed]

### 16.2 HYOSCYAMUS NIGER AND ATROPINE – CLARIFICATION OF SCHEDULE 2 ENTRY

#### PURPOSE

The Committee considered correspondence questioning the Schedule 2 entry for *Hyoscyamus niger* and atropine, in particular the cut-off for divided preparations.

#### BACKGROUND

A Committee member drew to the Secretariat's attention, a possible transcription error in the outcome from the February 2002 NDPSC Meeting when the Committee made recommendations amending the scheduling of solanaceous plants and alkaloids, including *Atropa belladonna*, atropine, *Datura spp*, *Datura stramonium*, *Datura tatula*, *Duboisia leichhardtii*, *Duboisia myoporoides*, hyoscine, hyoscyamine and *Hyoscyamus niger*.

In respect to *Hyoscyamus niger*, a member noted, that in February (2002), the Committee created a 30 mcg cut-off to unscheduled but in that part of the entry for divided preparations, it appeared that the dose had been set too low. The entry read "in divided preparations containing 0.03 mg of total solanaceous alkaloids or less..... recommended daily dose 1.2 mg ...." It was further noted that this meant that the tablet had 30 mcg but was stated that up to 1200 mcg could be taken. The entry should therefore be 0.3 mg per dose in the undivided form.

At the November 2001 meeting of NDPSC, the Committee agreed to the following principles for inclusion of preparations containing solanaceous plants and alkaloids (excluding hyoscine hydrobromide) in Schedule 2.

- Plants and Alkaloids: (i) In undivided oral preparations containing  $\leq 0.03\%$  of alkaloids, when labelled with a dose of  $\leq 0.3$  mg of alkaloids per dose and a maximum recommended daily dose of  $\leq 1.0$  mg of alkaloids.
- (ii) In divided oral preparations containing  $\leq 0.3$  mg of alkaloids per dose, when labelled with a maximum recommended daily dose of  $\leq 1.0$  mg alkaloids.
- (iii) In other preparations for external use (eg plasters, etc), 0.03% alkaloids.
- “Smoking and burning exemption” where appropriate.
- For hyoscine transdermal patches,  $\leq 2$  mg per dosage unit.
- Belladonna and hyoscyamine in preparations for external use: 0.03% alkaloids.
- The S2 entry for atropine preparations appropriately labelled for OP poisoning remained appropriate.
- Current general exemption of 10 mg/kg or 10 mg/L for homeopathic preparations remains appropriate.

This decision was based on the grounds that the products listed in the ARTG for OTC use containing solanaceous plants and alkaloids were considered to be within currently established dose levels and supported by long history of use and post-marketing clinical experience.

Having regard to the principles established by the Committee, it appeared that the Schedule 2 entry for divided preparations of products containing *Hyoscyamus niger* should have read “in divided preparations containing **0.3 mg** of total solanaceous alkaloids or less .....and **not 0.03 mg** of total solanaceous alkaloids ..... It also appeared that this translation error had also been made in respect to atropine.

## DISCUSSION

The Committee noted that the records of previous NDPSC discussion relating to solanaceous alkaloids confirmed that a translation error had been made in the Minutes of the 2001 NDPSC meeting which had gone unnoticed until this time.

The entries for atropine and *Hyoscyamus niger* in the New Zealand classification further confirmed the view that the cut-off for divided preparations should be 0.3 mg.

## DECISION 2004/42 – 26

The Committee noted the transcription errors and agreed to editorially amend the entries for *Hyoscyamus niger* and atropine in accordance with the principles established by the Committee for inclusion of preparations containing solanaceous plants and alkaloids in Schedule 2 and to include these amendments in SUSDP Amendment 2.

**Schedule 2 – Editorial amendment (For inclusion in SUSDP 19/2 – effective 1 January 2005)**

ATROPINE – Amend entry to read:

ATROPINE (excluding atropine methonitrate):

- (a) for oral use:
  - (i) in undivided preparations containing 0.03 per cent or less of total solanaceous alkaloids when labelled with a dose of 0.3 mg or less of total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or
  - (ii) in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or
- (b) preparations containing atropine sulfate when packed and labelled for the treatment of organophosphorus poisoning:
  - (i) in tablets each containing 0.6 mg or less of atropine sulfate in packs of 20 tablets; or
  - (ii) in preparations for injection each containing 0.6 mg per mL or less of atropine sulfate in packs of five.

HYOSCYAMUS NIGER – amend entry to read:

HYOSCYAMUS NIGER for oral use:

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

### **16.3-16.4      2,5-DIMETHOXY-4-IODOPHENETHYLAMINE AND 5-METHOXY- $\alpha$ -METHTRYPTAMINE**

#### **PURPOSE**

The Committee considered the inclusion of entries for 2,5-dimethoxy-4-iodophenethylamine (2C-I) and 5-methoxy- $\alpha$ -methtryptamine (5-Meo-AMT) in Schedule 9 of the SUSDP.

#### **BACKGROUND**

The XXXXXXXXXX identified two substances, 2C-I and 5-Meo-AMT, that have the potential to be abused. The XXXXXXXXXX asked that the Committee consider these substances for inclusion in Schedule 9 of the SUSDP.

#### **DISCUSSION**

The Committee noted the following:

- The XXXXXXXXXX submitted an extract of an article from the *Economist* detailing the emergence of a new illegal party drug referred to as 2C-I. The European Union has decided to impose control measures and criminal penalties in respect of 2C-I and other psychotropic substances. Information on the internet is widely available and suggest that 2C-I is gaining popularity in the UK as a dance drug and is described as the substance most likely to be “the next ecstasy”. Furthermore, 2C-I is available on the internet from specialist chemical manufactures.
- In response to a seizure of a new mind altering drug, 5-meo-AMT, in South Australia, the XXXXXXXXXX sought advice from the XXXXXXXXXX as to whether there was scope in XXXXXXXXXX legislation to control the substance. The XXXXXXXXXX sought advice from the XXXXXXXXXX as to whether 5-methoxy- $\alpha$ -methtryptamine is a derivative of N,N-diethyltryptamine (DET), 3-(2-dimethylaminoethyl)-4-hydroxyindole (psilocine or psilotsin), N,N-dimethyltryptamine (DMT) or psilocybine and thus included in Schedule 9 of the SUSDP. The FSST advised that 5-Meo-AMT is not a derivative of any substance currently listed in Schedule 9 and is therefore not a prohibited substance.

Consequently, the XXXXXXXXXX requested that the Committee consider foreshadowing the include an entry for 2C-I and 5-Meo-AMT in Schedule 9 of the SUSDP.

Members noted that the European Union had also decided to impose control measures and criminal penalties in respect of other phenethylamine analogues such as 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2) and 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7).

Members were advised that preliminary investigations suggested these substances were used as synthesis precursors and that there did not appear to be any large-scale industrial use.

The XXXXXXXXXX Member expressed concern that the industrial applications of these substances had not been fully determined. Accordingly, the member proposed that PACIA be consulted prior to the foreshadowed decision being confirmed at the next NDPSC meeting.

A member suggested that perhaps a class entry may be more appropriate on the grounds that it would encompass not only these substances but also any future derivatives. The member was advised that entries for specific substances, particularly in the more restrictive schedules containing substances of abuse, eliminated the need for interpretation by law enforcement agencies and others and may also serve to expedite prosecutions for possession, trafficking, etc.

A member advised the Committee that the *Model Criminal Code, Chapter 6 – Serious Drug Offences* includes a section entitled "Substances that are controlled drugs" and discusses how to define which substances are covered by legislation. The Committee agreed that this document may be of value to future considerations and that it should be obtained and provided for consideration at the February 2005 meeting.

The Committee was of the opinion that there was sufficient evidence to suggest that these substance did exhibit the potential for abuse and, therefore, warranted control through scheduling.

## OUTCOME

The Committee agreed to foreshadow the inclusion of entries for 2,5-dimethoxy-4-ethylthiophenethylamine, 2,5-dimethoxy-4-iodophenethylamine, 2,5-dimethoxy-4-(n)-propylthiophenethylamine and 5-methoxy- $\alpha$ -methtryptamine in Schedule 9 of the SUSDP on the basis of their abuse potential.

## FORESHADOWED DECISION (for consideration at February 2005 meeting)

### Schedule 9 – New Entries

2,5-DIMETHOXY-4-ETHYLTHIOPHENETHYLAMINE (2C-T-2).

2,5-DIMETHOXY-4-IODOPHENETHYLAMINE (2C-I).

2,5-DIMETHOXY-4-(N)-PROPYLTHIOPHENETHYLAMINE (2C-T-7).

5-METHOXY- $\alpha$ -METHTRYPTAMINE (5-Meo-AMT).

[Items removed]

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

**17.1 NICOTINE**

**PURPOSE**

The Committee considered a proposal to require the warning statement “KEEP OUT OF REACH OF CHILDREN” on exempt Nicotine Replacement Therapy (NRT) products.

**BACKGROUND**

The October 2003 Meeting agreed to exempt nicotine in chewing gum and transdermal patches for Nicotine Replacement Therapy (NRT) from scheduling requirements to harmonise with New Zealand (effective 1 May 2004). Additionally, the February 2004 meeting agreed to exempt nicotine lozenges for NRT from scheduling requirements (effective 1 September 2004). Scheduled NRT preparations include those for inhalation (S2) or sublingual use (S2 effective from 1 January 2005) and nasal administration (S4).

The NDPSC received correspondence from the OTC Medicines Section advising that the Medicines Evaluation Committee (MEC) had recommended that the NDPSC consider requiring the warning “KEEP OUT OF REACH OF CHILDREN” on all unscheduled NRT preparations, i.e. chewing gum, preparations for transdermal use and lozenges. MEC had noted that, whilst scheduled NRT products were required to include this warning on the label, there was no such requirement for unscheduled or exempt NRT products. Furthermore, MEC had recommended that the warning statement be prominently placed on the main label of the primary pack and to be written in capital letters on the first line.

The Committee also received advice that a consequential amendment was required for nicotine in Appendix F, Part 3 of the SUSDP, to reflect the deletion of the Schedule 3 entry agreed to at the June 2004 meeting.

**DISCUSSION**

The Committee noted that the “KEEP OUT OF THE REACH OF CHILDREN” cautionary statement in bold lettering and prominently displayed in conjunction with the signal heading was associated with the scheduling of products. Members, however, considered this would not preclude the cautionary statement being required as a condition of registration and displayed elsewhere on the label in lower case lettering. Accordingly, members were not in favour of using the “KEEP OUT OF THE REACH OF CHILDREN” cautionary statement if the product was not scheduled.

The Committee also recalled that, in considering unscheduled nicotine products, the Committee had considered the poisoning potential for children. Based on considerable data, the Committee had agreed that poisoning in children was unlikely and therefore a warning statement highlighting the need to keep the product out of the reach of children was not necessary. No further information had been presented to change that view.

A member expressed the view that the issue had raised a wider policy issue relating to whether, for consistency, exempt analgesics should also have the cautionary statement “KEEP OUT OF THE REACH OF CHILDREN”. The consensus of Members was that widespread use of such a statement on exempt products could dilute the effectiveness of the warning statement.

## **OUTCOME**

The Committee agreed that it would thank MEC for raising the issue but stress that the toxicological profile of the products of interest was such that the warning statement “KEEP OUT OF THE REACH OF CHILDREN” in bold lettering and prominently displayed on the main label of the primary pack was not warranted or favoured. However, the Committee also agreed to advise MEC that it would have no objection if the statement was added as a condition of registration elsewhere on the label, but not in bold lettering.

## **DECISION 2004/42 – 27**

The Committee also agreed to make a consequential amendment to the entry in Appendix F, Part 3 for nicotine to reflect the deletion of the Schedule 3 entry at the June 2004 meeting.

### **Appendix F, Part 3 – Editorial Amendment (For inclusion in SUSDP 19-2)**

Nicotine – amend entry to read:

Nicotine except when in tobacco or Schedule 2

Safety Directions .....1,4

## **17.2 QUININE**

### **PURPOSE**

The Committee considered Medicines Evaluation Committee’s (MEC) recommendation to include all quinine-containing preparations in Schedule 4 (S4).

## BACKGROUND

Quinine is available in Australia as quinine bisulphate and quinine sulphate for oral use and quinine dihydrochloride for iv use. The approved indications include the treatment of, or symptomatic relief of, nocturnal cramps and/or muscle cramps, and for the treatment of malaria.

The August 2003 ADRAC Meeting noted that 598 adverse reactions reports were received with quinine, including 13 reports with a fatal outcome. Thrombocytopenia was described in 214 quinine reports of thrombocytopenia with quinine, including 4 reports with a fatal outcome; in 153 of these reports, quinine was the sole suspected medicine. Other haematological reactions reported included neutropenia (25 reports), pancytopenia (6), aplastic anaemia (2) and agranulocytosis (7) and of these, fatal outcomes were reported with pancytopenia (2 reports), aplastic anaemia (1) and agranulocytosis (1). Other reports with fatal outcomes included abnormal hepatic function (1 report), hepatic failure (1), hepatocellular damage (1) and cardiac failure (1). Other potentially serious reports included hepatitis (24 reports), abnormal hepatic function (20), and various skin reactions, including urticaria (18).

The February 2004 NDPSC Meeting noted that the ADEC October 2003 meeting considered a proposal from ADRAC to remove all indications for quinine-containing products except malaria, on the basis of unfavourable risk/benefit ratio for other indications. The ADEC agreed with ADRAC and accordingly made a recommendation to the NDPSC to include all quinine preparations in S4 of the SUSDP. This decision was based on concerns with regard to the apparent link between products containing quinine and thrombocytopenia, and that use of quinine for any treatment, other than malaria, was not evidence-based. The NDPSC also noted that the TGA, based on ADEC's advice, had advised sponsors of prescription products that all indications other than malaria would be deleted from all quinine-containing products as at January 2004. One registered OTC product (XXXXXXXXXX) containing 15 mg quinine (maximum daily dose of 45 mg) and indicated for "to alleviate the unpleasant withdrawal symptoms normally experienced when giving up smoking" had remained unaffected (unscheduled) by the recent scheduling amendment to quinine. The NDPSC was advised that the sponsor of XXXXXXXXXXXX (XXXXXXXXXX) had been requested to provide data for consideration by MEC to support the safety of this product in relation to the potential for quinine to cause severe haematological reactions.

A pre-meeting submission was received from XXXXXXXXXXXX, who was acting on behalf of the registered sponsor for XXXXXXXXXXXX, XXXXXXXXXXXX, advising that XXXXXXXXXXXX was registered on the ARTG as an outcome of a conciliation before the AAT. In addition, CL sought approval to submit a late pre-meeting comment as their client had only become aware of the proposal and had asked that the NDPSC defer the consideration of quinine to a later date. The Secretariat had responded to XXXXXXXXXXXX advising that the NDPSC would not object to their submission of supporting materials relating to the gazetted quinine scheduling proposal for



consideration at the October 2004 meeting. An outline of the NDPSC public consultation process was also covered in the Secretariat's letter. A late submission was received from XXXXXXXXXX on 12 October 2004.

## DISCUSSION

The Committee noted a Minute received from OTC Medicines Section in response to the NDPSC's request for MEC to comment on the amendment to the scheduling of quinine made at the February 2004 meeting. The Committee also noted the June 2004 MEC minutes of the meeting and background papers on quinine that had been provided to the NDPSC for information. The following issues were discussed in the MEC Minutes:

- The sponsor in its response to the TGA cited the following:
  - (a) The amount of quinine ingested from XXXXXXXXXX was similar to that from tonic water;
  - (b) Cases of thrombocytopenia reported to ADRAC involved higher doses of quinine (200-600 mg); and
  - (c) There had been few reports, worldwide, of adverse effects from use of XXXXXXXXXX.
- MEC had noted that the data available suggested a very small risk of thrombocytopenia with quinine in doses of less than 200 mg. However, although the sponsor had suggested a dose-threshold for quinine-induced thrombocytopenia, no specific evidence of such a dose-threshold relationship had been provided or found. A MEC member had noted that whilst thrombocytopenia occurred infrequently with quinine, it could be fatal, and significant morbidity was associated with quinine-induced thrombocytopenia. In these circumstances, a satisfactory risk/benefit ratio would depend on good evidence of efficacy and, given the doubtful evidence for XXXXXXXXXX's efficacy, the risk/benefit profile of this product was considered to be unfavourable.
- The MEC made the following recommendations:
  - (a) Noting that satisfactory evidence had not been provided to establish that the quinine in XXXXXXXXXX provides or contributes to XXXXXXXXXX's putative efficacy in alleviating withdrawal symptoms experienced when giving up smoking, MEC agreed that XXXXXXXXXX should be removed from the ARTG on the basis of its unfavourable risk vs. benefit ratio. The committee also agreed to recommend to the NDPSC that all quinine-containing products should be included in S4 of the SUSDP because quinine is not suitable for use without the advice of a medical practitioner due to its unfavourable risk vs. benefit ratio.

The MEC minutes also discussed the TGA review of the safety of quinine in OTC products noting the following issues:

- Quinine was included in pregnancy Category D2, and that cinchonism may occur after therapeutic doses of quinine, or after low doses in susceptible individuals.
- Quinine did not induce antibodies in the ‘traditional’ manner, whereby a drug binds covalently to membrane glycoproteins and functions as a hapten to induce antibody responses. Instead, quinine binds non-covalently to membrane glycoproteins, so its continuing presence is required for the immune response. The immunologic mechanism of quinine-associated thrombocytopenia suggested that there may be no dose threshold below which the effect does not occur; however, no confirmed cases were found at known doses below 200 mg (although many reports did not include sufficient dosage information). The review suggested several possible reasons for the lack of reports of thrombocytopenia associated with lower doses of quinine, and noted that the lack of reports did not specifically preclude such an association.
- The sponsor had not provided any scientific evidence to support their claim that “thrombocytopenia is dose-related” nor did they provide up-to-date post-marketing data on XXXXXXXXXX. The sponsor stated that the recommended dose of XXXXXXXXXX provided a similar quinine intake to that from 500 mL or less of tonic water, and that thrombocytopenia had been reported after exposure to quinine in relatively large quantities of tonic water or bitter lemon (>1 litre). (The maximum permitted level of quinine in tonic water, bitter lemon and quinine drinks is 100 mg/kg and a maximum of 300 mg/kg quinine is allowed in wine and other beverages [*Food Standards Code*]).
- The NDPSC in 1998 considered a submission on behalf of XXXXXXXXXX, to reschedule quinine to allow the exemption of XXXXXXXXXX from the requirements of scheduling. The TGA review noted that the submission to the NDPSC included the same arguments as those raised in the sponsor’s 2004 letters to the TGA. Neither did the submission to the NDPSC or the sponsor’s current responses provide specific evidence of a dose-threshold for quinine-induced thrombocytopenia.
- The MEC June 1999 meeting had recommended rejection of the application to register XXXXXXXXXX, as the data provided by the sponsor (two clinical trials) did not adequately support the efficacy and safety of the product. However, whilst the MEC recommendation was upheld by the Minister, it was overturned after an appeal to the Administrative Appeals Tribunal (AAT). XXXXXXXXXX was registered with the ARTG indications “XXXXXXX is designed to alleviate the unpleasant withdrawal symptoms normally experienced when giving up smoking”.
- In response to the TGA’s 2004 request to justify the safety of XXXXXXXXXX, the sponsor referred to testimonials from satisfied Australian customers, and to the product’s status as “*an approved therapeutic medicine*” in 12 countries. The author of the TGA Review considered, however, that evidence for the efficacy of XXXXXXXXXX was doubtful and on this basis concluded that XXXXXXXXXX’s risk vs. benefit profile was unfavourable.

The Committee noted that high dose quinine products including those registered for cramps had been removed from the market with the only quinine products remaining

being those for the control of malaria. These products were now included in Schedule 4. There was an exemption for preparations containing 50 mg or less of quinine per recommended daily dose. The central issue for the Committee to consider was whether XXXXXXXXXX containing 15 mg quinine with a maximum recommended dose of 45 mg/day presented a possible exposure risk which required scheduling. Issues relating to efficacy and possible adverse effects were considered by the Committee to be registration-related matters and therefore should be dealt with by the TGA.

The Committee noted, however, that the pre-meeting submission from XXXXXXXXXX had highlighted the fact that the TGA was now satisfied as to the safety of the product and accordingly had been prepared to consent to a decision approving the application. The submission also addressed the toxicity and safety of quinine, particularly in the context of its use in the XXXXXXXXXX product (with a dose of up to 45 mg/day) and in comparison with prescription medicines containing quinine for nocturnal leg cramps (which had now been removed from the market) and malaria where doses of up to 300 mg/day were recommended for nocturnal leg cramps and up to 1800 mg/day in adults for malaria. The submission also addressed the question of safety in the context of smoking and the health benefits of stopping smoking which XXXXXXXXXX considered weighed heavily towards the overall benefits associated with the use of XXXXXXXXXX.

The Committee also noted that drinks containing quinine (up to a maximum of 300 mg/kg) were available and that any scheduling decision would not impact on the Food Standards Code. The issue of quinine in foods had been brought to the attention of Food Standards Australia New Zealand (FSANZ). FSANZ had been invited to comment on the proposal however a submission was yet to be received.

The Committee noted that in relation to drinks, the presence of quinine was highlighted on labels. It agreed to suggest to MEC that drawing on this analogy, they might give consideration to highlighting the presence of quinine on labels of exempt medicinal products containing quinine.

## OUTCOME

The Committee noted the MEC assessment of the safety of quinine in OTC products and the possibility of quinine-induced thrombocytopenia. However, as the risk of such an adverse effect associated with low doses (ie a 50 mg daily intake of quinine or less) was not known, the Committee agreed that the current scheduling of quinine remained appropriate.

Additionally, the Committee agreed to maintain a watching brief with regard to low dose quinine.

[Item removed]

**18. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND****18.1 ZINC COMPOUNDS****PURPOSE**

The Committee considered the AREDS Study which recommended that the intake of high levels of antioxidants and zinc significantly reduced the risk of advanced age-related macular degeneration (ARMD).

**BACKGROUND**

The XXXXXXXXXX Member requested that the AREDS Study be included on the agenda of the June 2004 NDPSC meeting. Discussion was deferred until the October 2004 meeting.

In response to the increasing public health concern regarding widespread use of high-dose vitamins and minerals for age-related macular degeneration, the US National Eye Institute (NEI), sponsored a major clinical study called The Age-Related Eye Disease Study (AREDS). The AREDS was designed to:

- Assess the clinical course, prognosis, and risk factors of ARMD and cataract.
- Evaluate the effects of high doses of antioxidants and zinc on the progression of ARMD and vision loss; and
- Evaluate the effects of high doses of antioxidants on the development and progression of cataract and vision loss.

The AREDS included two clinical trials. Trial 1 related to ARMD and Trial 2 related to cataract. Both trials generally shared one pool of participants. 4,757 participants aged 55-80 years participated in the study. Because 1,117 participants did not have at least early stages of ARMD, the ARMD trial included only the 3,640 participants who had at least early ARMD. The cataract results were based on 4,629 participants; 128 of the 4,757 participants had cataract surgery on both eyes prior to participation in the study and therefore were ineligible for the cataract clinical trial.

The participants' stages of disease ranged from no evidence of ARMD in either eye, to advanced ARMD with vision loss in one eye but good vision (at least 20/30) in the other eye. The participants were enrolled in 11 clinics nationwide. Fifty-six percent were female; the median age was 69 years. The study commenced in November 1992 and ended in January 1998. About 90 percent of all participants were followed for a minimum of five years.

Depending on their stages of ARMD, the AREDS participants were placed in one of four categories.

- Category One; participants had no ARMD and a few small or no drusen (tiny yellow deposits in the retina) in either eye.
- Category Two; participants had early ARMD, either several small drusen or a few medium-sized drusen in one or both eyes.
- Category Three; participants had intermediate ARMD, either many medium-sized drusen or one or more large drusen in one or both eyes. These participants were at high risk for developing advanced ARMD, which is generally defined as either a break-down of light-sensitive cells and supporting tissue in the central retinal area (advanced dry form), or abnormal and fragile blood vessels under the retina (wet form).
- Category Four participants already had advanced ARMD in one eye, and in the other eye had good vision with no sign of advanced ARMD. Previous studies had shown that the eye without ARMD was at high risk for developing advanced ARMD.

The participants in each category were randomly selected to receive daily oral tablets for one of four treatments: 1) zinc alone; 2) antioxidants alone; 3) a combination of antioxidants and zinc; or 4) a placebo. The antioxidant formulation contained a combination of vitamin C, vitamin E, and beta-carotene. The specific daily amounts of antioxidants and zinc used by the AREDS researchers were 500 milligrams of vitamin C; 400 international units of vitamin E; 15 milligrams of beta-carotene; 80 milligrams of zinc as zinc oxide; and two milligrams of copper as cupric oxide.

The Study concluded that people at high risk for developing advanced ARMD, ie those with intermediate ARMD, and those with advanced ARMD in one eye only, reduced their risk of developing advanced stages of ARMD by about 25 percent when treated with the combination of "antioxidants plus zinc." The combination of "antioxidants plus zinc" was also assessed to reduce the risk of central vision loss by 19 percent in the same group. Participants at high risk for developing advanced ARMD who were treated with "zinc alone" reduced their risk of developing advanced ARMD by about 21 percent and their risk of vision loss by about 11 percent. Participants who were treated with "antioxidants alone" reduced their risk of developing advanced stages of ARMD by about 17 percent and their risk of vision loss by about 10 percent.

<b>Antioxidants Plus Zinc Alone</b>	<b>Zinc Alone</b>	<b>Antioxidants</b>
<ul style="list-style-type: none"> <li>• Reduced risk of developing advanced ARMD by about 25 percent</li> <li>• Reduced risk of vision loss by about 19 percent</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced risk of developing advanced ARMD by about 21 percent</li> <li>• Reduced risk of vision loss by about 11 percent</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced risk of developing advanced ARMD by about 17 percent</li> <li>• Reduced risk of vision loss by about 10 percent</li> </ul>

The study was not designed to evaluate the effect of the antioxidants and zinc in study participants who initially had no ARMD (Category One). This is because previous studies had indicated that people aged 60 and over with no ARMD have a very low risk for developing a clear progression of ARMD within a seven-year period (the life of the AREDS clinical trial). The Age-Related Eye Disease Study confirmed this low risk.

For those study participants who initially had early ARMD (Category Two), the antioxidants and zinc used by the AREDS researchers did not slow the disease's progression to intermediate ARMD. Consequently, there is no apparent need for those diagnosed with early ARMD to take the combination studied in the AREDS. However, for those with early ARMD, the NEI has recommended that they receive dilated eye examinations every year to determine if the disease is progressing.

Following the June 2004 NDPSC meeting, pre-meeting Gazettal sought comment on the foreshadowed proposal to increase the cut-off for unscheduled preparations for human internal use.

## DISCUSSION

Members noted that advice was sought from the XXXXXXXXXX Member as to whether it is proposed (in New Zealand) to make the AREDS formulation or mineral supplement products containing 80 mg of Zinc available on an OTC basis (General sales or Pharmacy Only). The member advised the Committee that the matter was yet to be considered by the MCC.

The Committee noted the risk assessment for zinc that was undertaken by the UK Expert Group on Vitamin and Minerals and published in 2003. The study concluded that:

*“Consumption of zinc supplements by human volunteers has been reported to cause gastrointestinal effects, including cramping and nausea. This was particularly apparent when the supplements were taken with little or no food.*

*Excess levels of dietary zinc interfere with the gastrointestinal absorption of copper, potentially leading to secondary copper deficiency. Signs of this include decreased ESOD (erythrocyte superoxide dismutase) activity, increased LDL cholesterol and decreased HDL cholesterol, decreased glucose clearance and abnormal cardiac function. One of the most sensitive markers of this appears to be ESOD activity. Supplemental doses of 50 mg cause significant decreases in the activity of this enzyme.*

*Iron and zinc in the diet each affect the gastrointestinal absorption of the other. Few data are available, but high levels of iron are known to interfere with zinc uptake, and more limited data suggest that the reverse interaction also occurs. This has not been considered in detail.*

*Two vulnerable groups have been identified; diabetics, since the study by Cunningham et al. (1994) indicates that HbA1c is increased in conditions of zinc excess, and sufferers of haemochromatosis who have enhanced gastrointestinal absorption of iron, cobalt, lead and possibly zinc, potentially predisposing them to accumulation of zinc. However, there are insufficient data to establish the level of zinc intake at which adverse effects could occur in these groups.*

*Data are also available from animal studies that indicate high zinc levels can have a negative effect on copper balance. These have not been considered in detail in the risk assessment, as considerable data from human studies are available.*

### **ESTABLISHMENT OF SAFE UPPER LEVEL**

*Key studies: Yadrick et al. (1989), Fischer et al. (1984), Black et al. (1988), Cunningham et al. (1994), Davis et al. (2000).*

*LOAEL: 50 mg/day*

*Uncertainty factor: 2 (LOAEL to NOAEL extrapolation).*

*Safe Upper Level:  $50/2 = 25$  mg zinc/day for supplemental zinc for daily consumption over a lifetime.*

*Zinc affects iron and copper uptake at supplemental doses of 50 mg/day and above. However, this is not apparent in all studies. The key endpoint is the reduction of copper absorption by zinc. Where the contribution of dietary zinc was also assessed, the lowest level at which effects were apparent (reduced activity of the copper-dependent enzyme ESOD being the most sensitive) was approximately 58-62 mg/day (50 mg supplements plus approximately 8-12 mg/day from food). There is no evidence of adverse effects from dietary zinc intake. In addition, since the contribution of zinc from the diet in many of the studies is uncertain, and may have been altered under study conditions, it is appropriate to set a safe upper level for supplemental zinc but not total intake. Taking the LOAEL as 50 mg/day and by applying an uncertainty factor of 2 to account for LOAEL to NOAEL extrapolation, a Safe Upper Level of  $50/2 = 25$  mg/day for supplemental zinc is derived (equivalent to 0.42 mg/kg bw/day in a 60 kg adult). An uncertainty factor of 2 has been used rather than 3 since the effect concerned is a small and inconsistent change in a biochemical parameter. No uncertainty factor is needed for inter-individual variability because this safe upper level is supported by a large number of human studies. Assuming a maximum intake of 17 mg/day from food, a total intake of 42 mg/day (equivalent to 0.7 mg/kg bw/day in a 60 kg adult) would not be expected to result in any adverse effects."*

In response to the pre-meeting Gazetial of the foreshadowed proposal to amend the cut-off levels, comment was received from XXXXXXXXXX and XXXXXXXXXX. Both

respondents made no specific comment but noted an interest in zinc compounds and the Committee's consideration of the issue. Both reserved the right to make further post-meeting comments.

Members noted that no submission or comments had been received from professional bodies. Accordingly, the Committee agreed that comment regarding the AREDS Study should be sought from the Therapeutic Committees of the Royal Australasian College of Physicians and the Royal Australasian College of Ophthalmologists. Specifically, it was proposed that comment should be sought on the implications of increasing the allowable daily intake of zinc for general sales to levels identified as having a beneficial effect in the AREDS Study.

The TGA Member advised the Committee that Australia helped prepare the IPCS Monograph for zinc (No. 221, 2001) and suggested that it may be of assistance when the matter is further considered by members at the next meeting.

## OUTCOME

The Committee agreed to defer consideration of this matter in order to allow further advice to be obtained.

[Items removed]

## 22.1 EDITORIALS AND ERRATA

### PURPOSE

The Committee considered a number of editorial changes and errata to the SUSDP.

### BACKGROUND

In October 2003, the XXXXXXXXXX Member (XXXXXXXXXX) identified a number of editorial corrections to be made to the SUSDP. In April 2004, the former XXXXXXXXXX Member proposed further editorial corrections as follows:

Schedule 2		
ASPIRIN	Delete reference to additional actives in the italics at the end of (b)(ii)(B) and (c)(iii)(B)	See Agenda Item 13.4
ATROPINE	Clause (a)(ii) replace "0.03 mg" with "0.3 mg"	See Agenda Item 16.2



DUBOISIA LEICHARDTII	Amend substance name to read DUBOISIA LEICHHARDTII Clause (b) insert “per dosage unit” after “total solanaceous alkaloids” (in line with duboisia myoporoides)	
HYOSCYAMUS NIGER	Clause (b) replace “0.03 mg” with “0.3 mg or less”	See Agenda Item 16.2

<b>Schedule 3</b>	
SODIUM PICOSULFATE	Delete “,” after “diagnostic”

<b>Schedule 4</b>	
ETHOHEPTAZINE CITRATE	Amend to read ETHOHEPTAZINE
MONOBENZONE	Replace “or other alkyl ethers” with “and other alkyl ethers”
PARACETAMOL	Clause (a) replace “in the Schedules” with “in these Schedules”

## DISCUSSION

The Committee noted that errata and editorial amendments to the aspirin, atropine and *Hyoscyamus niger* scheduling entries were considered separately at agenda items 13.4 and 16.2 respectively.

A member questioned the correct botanical spelling of *Duboisia leichhardtii* and requested that this be checked before any changes were made to the SUSDP entry.

## DECISION 2004/40 – 28

The Committee agreed to include errata and editorial amendments in SUSDP 19/2 for *Duboisia leichhardtii*, sodium picosulfate, ethoheptazine, monobenzone and paracetamol.

## EDITORIAL AMENDMENTS AND ERRATA

### Schedule 2 – Amendment

DUBOISIA LEICHARDTII – amend entry to read:

DUBOISIA LEICHHARDTII for oral use:

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

- (b) in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids.

### **Schedule 3 – Amendment**

SODIUM PICOSULFATE – amend entry to read:

SODIUM PICOSULFATE in preparations for oral use for bowel cleansing prior to diagnostic medical or surgical procedures.

### **Schedule 4 – Amendments**

ETHOHEPTAZINE CITRATE – amend entry to read:

ETHOHEPTAZINE.

MONOBENZONE – amend entry to read:

MONOBENZONE and other alkyl ethers of hydroquinone for human therapeutic use or cosmetic use.

PARACETAMOL – amend entry to read:

PARACETAMOL:

- (a) when combined with aspirin, caffeine or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;
- (b) in tablets or capsules containing more than 665 mg of paracetamol; or
- (c) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol.