Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

44th Meeting
21-23 June 2005

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GLOSSARY

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

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

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

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

1.7 PROCEDURAL MATTERS

1.7.1 OPERATIONS/POLICIES OF THE COMMITTEE

1.7.1.2 SPONSOR ACCESS TO EVALUATION REPORTS

PURPOSE

The Committee considered the provision of NDPSC evaluation reports to sponsors for comment prior to the NDPSC meeting.

BACKGROUND

At the February 2004 meeting, the Committee considered a proposal from XXXXXXXX seeking the release of evaluation reports to the sponsor so that comment can be submitted prior to NDPSC consideration of the matter. The Committee requested that the Secretariat review the proposal and identify implications of providing the evaluator's reports to the applicant prior to the NDPSC decision.

At the February 2005 NDPSC meeting the Secretariat advised that it was not opposed to release of the evaluation reports but highlighted that it would add an additional administrative burden. Members noted that currently, the cut-off for receipt of rescheduling applications is 16 weeks prior to the NDPSC meeting. This allows time for the submission to be despatched, assessed (around 8 weeks) and for the evaluation report to be included in the first batch of papers to the members. The Secretariat advised that, allowing time for these processes, an additional pre-meeting comment on evaluation reports will require rescheduling submissions to be made at least 20 weeks prior to the NDPSC meeting. This extra time would be required to obtain reports from the evaluators, distribute these reports to the sponsor companies and allow them reasonable time to comment.

The Committee was of the view that the provision of reports to sponsors would be beneficial to the scheduling process and prepared the following model:

- Rescheduling submissions must be made 20 weeks before an NDPSC meeting;
- Evaluation reports will be distributed to the sponsor company (applicant) with personal information, such as the evaluator's name etc., deleted;
- Companies will have a maximum of 10 working days to comment. Responses are to be limited to 6 single sided A4 pages and in a font no smaller than 12 point. The response may only address issues raised in the evaluation report and must not contain any new or additional data.
- Consideration could be given to maintaining the current 16 week cut-off for receipt of submissions if an applicant was willing to forfeit access to the evaluation report.

The Committee noted that this proposal would involve a change to the Committee's guidelines and would require the National Coordinating Committee of Therapeutic Goods (NCCTG) approval. The Committee agreed, in the interests of maintaining transparency and consistency with other expert committees, that the proposed model for accessing evaluator's reports be referred to NCCTG for consideration.

DISCUSSION

The Committee was advised that the proposed model was referred to the April 2005 meeting of the NCCTG. The Committee noted that it was the Secretariat's understanding that NCCTG supported in principle the provision of evaluator reports to applicants prior to NDPSC meetings and supported this change being implemented for the February 2006 NDPSC meeting. The Committee further noted that this would mean that the cut off for scheduling applications for the February 2006 NDPSC meeting would be 7 October 2005.

A Member noted that the proposed model would lead to increased transparency and committee efficiency because if sponsors have an opportunity to comment early on the evaluators report then the Committee would get to consider that comment at the meeting, as opposed to a post-meeting comment being consideration at the subsequent meeting.

The Members also noted that the proposed model was restricted to medicines scheduling applications at this time.

The Committee were advised that the Secretariat had sought, on behalf of the Committee, comment from XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX about this proposal.

The Committee noted that XXXXXXXX supported the proposed model and the implementation date. The Committee also noted that XXXXXXXX hoped that with the experience gained from early implementation of the proposed model, the NCCTG will be able to give consideration to a review of the lead timeframes under the new joint agency arrangements. Members were advised that XXXXXXXX asked for clarification on:

- How the evaluation reports will be disseminated? XXXXXXXX requested that, to allow the maximum response time of 10 working days, the Secretariat email or fax evaluation reports, in addition to hard copy being sent by mail, as mail is often delayed.
- Will the evaluation reports be available to sponsors early in the agenda gazettal period?

The Secretariat indicated that the request for email or fax dissemination of evaluation reports was considered reasonable and advised that the Secretariat was willing to implement this procedure. There was general agreement to this procedural change by the Members.

The Committee noted that the timing of availability of evaluation reports was variable depending on the workload of the evaluator. The Secretariat agreed to provide evaluation reports to sponsors in a reasonable time frame following receipt from the evaluation, noting that it was necessary to remove personal information such as the evaluator's details.

The Committee further noted that XXXXXXXX and XXXXXXXX also supported the proposed model. The Members were advised that a response had yet to be received from XXXXXXXX.

A Member raised a possible scenario where, due to an unforeseen delay, there is not 10 days between receipt of the evaluation report and the NDPSC meeting. The Secretariat reassured the Committee that this was unlikely and that, at worst, the sponsor would have time to fax a comment for consideration at the NDPSC meeting.

The Committee also considered the maintenance of the current 16 week cut-off if an applicant was willing to forfeit access to the evaluation report. Following input from the Secretariat the Committee agreed that in cases where sponsors missed the 20 week cut-off they could negotiate with the Secretariat. This process would remain informal to allow flexibility and to avoid an additional administrative burden on the Secretariat.

OUTCOME

The Committee agreed to proceed with the proposed model for sponsor access to evaluation reports to allow implementation for the February 2006 meeting.

1.8 NDPSC WORKING PARTIES

1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY (MEDICINES)

1.8.1.1 MINUTES FROM TTHWP 13TH MEETING

The Committee noted the ratified Minutes from the 13th Meeting of the TTHWP held in February 2005.

1.8.1.2 MATTERS ARISING FROM THE 13TH MEETING

Matters arising from the 13th Meeting of the TTHWP were considered separately under agenda item 1.8.1.3.

1.8.1.3 MATTERS ARISING FROM NDPSC CONSIDERATION OF TTHWP ITEMS

1.8.1.3.1 AMPHOTERICIN

PURPOSE

The Committee considered harmonisation of scheduling of amphotericin with New Zealand having regard to advice from XXXXXXXX.

BACKGROUND

Amphotericin is a 'Prescription Only Medicine' in Australia and New Zealand but is also available in New Zealand as a 'Restricted Medicine' (S3) for the treatment of oral candidiasis. The Committee recalled that it had considered the harmonisation of amphotericin on several occasions, noting the potential for resistance development arising from any relaxation of scheduling in order to harmonise with New Zealand. The Committee had requested that the Secretariat arrange for a review of amphotericin for possible resistance.

The Secretariat advised that it had arranged for the review of possible resistance development to be undertaken by an expert. Literature searches had been undertaken to assist the reviewer but the review had not been able to be completed in time for the October meeting. It was expected that the review would be available to NDPSC at its February 2005 meeting. Accordingly, the Committee agreed to consider the amphotericin report and the possibility of resistance at its February 2005 meeting.

At the February 2005 meeting, the Committee was advised that the reviewer chosen to undertake the review had been unable to complete the task.

However, in the interim, it had been ascertained that there was only one amphotericin S3 product available in New Zealand, viz XXXXXXXX marketed by XXXXXXXX. XXXXXXXX had requested assistance from the XXXXXXXX member in approaching XXXXXXXX for advice on the level of use through pharmacies and whether it would support an S4 classification.

At the February 2005 meeting and in the absence of any response to date from XXXXXXXX, further consideration of the matter was deferred until the June 2005 meeting.

DISCUSSION

The Committee was informed that XXXXXXXX had recently advised that the New Zealand sponsor of XXXXXXXX, XXXXXXXX, had agreed that it would be appropriate for the scheduling of XXXXXXXX to be rescheduled in New Zealand to

Prescription Medicine status (Schedule 4). This would remove the difference between scheduling in Australia and New Zealand.

One member questioned whether the approach to the sponsor of XXXXXXXX in New Zealand with the proposal to reschedule amphotericin in New Zealand to achieve harmonisation was consistent with the agreed harmonisation procedures, particularly the need for gazettal to allow public comment. However the Committee recalled that this item was considered at the NDPSC 39th Meeting (October 2003) and that a pre-meeting submission had raised the possibility that more widespread use of amphotericin could lead to the development of resistance and therefore reduced effectiveness. Amphotericin had also been included in the pre-meeting gazette notice for the February and June 2004 NDPSC meetings. Therefore it was clear that gazettal and public consultation occurred. At that time, further discussion had been 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 which sought a detailed risk assessment. The recent advice from New Zealand to consider rescheduling amphotericin to 'Prescription Medicine' was consistent with resistance concerns and would be the subject of further consultation as part of New Zealand consultation processes. Consequently the Committee was satisfied that agreed trans-Tasman harmonisation processes had been followed.

OUTCOME

The Committee agreed that, having regard to the New Zealand advice that amphotericin would be considered for rescheduling to Prescription Medicine, the current scheduling of amphotericin in Australia remained appropriate.

The Committee further agreed that the matter should be formally referred to the New Zealand.

1.8.1.3.2 NICOTINE

PURPOSE

The Committee considered the foreshadowed decision (February 2005) to amend the scheduling of nicotine in order to harmonise the scheduling of nicotine sublingual tablets with New Zealand.

BACKGROUND

The February 2004 NDPSC meeting agreed to exempt from scheduling, nicotine lozenges for smoking cessation on the basis of experience with the availability of lozenges as a 'Pharmacy Only' medicine and the need to broaden options for smoking cessation. In the interests of harmonisation, the Committee had agreed that the MCC should be asked to consider including lozenges as a 'General Sales' medicine. This would result in harmonisation of scheduling for nicotine across all NRT product forms.

However, at the November 2004 meeting of the New Zealand Medicines Classification Committee, MCC recommended that nicotine in medicines, when in lozenges or sublingual tablets for smoking cessation, should be reclassified from pharmacy-only medicine to general sale medicine. As a result, the scheduling of sublingual tablets was unharmonised between Australia (S2) and New Zealand (general sale).

The February 2005 TTHWP meeting agreed that scheduling of the sublingual tablets should be harmonised with the most recent New Zealand decision ie that sublingual tablets to be exempt from scheduling.

The February 2005 Committee meeting agreed that, on the grounds of harmonisation with New Zealand, nicotine in sublingual tablets be exempt from scheduling requirements. To achieve harmonisation, the Committee foreshadowed amendments to the SUSDP for consideration at the June 2005 NDPSC meeting.

DISCUSSION

Since foreshadowing the amendments to achieve harmonisation, the Committee had received a submission from XXXXXXXX seeking scheduling harmonisation of the nicotine sublingual tablets with New Zealand. The XXXXXXXX submission noted that a search of MEDLINE, Embase and BIOSIS from March 2004 to March 2005 had found that in the past 12 months there had been no published reports relating to inappropriate use, abuse or misuse of nicotine sublingual tablets, no published reports of overdose or poisoning with nicotine sublingual tablets and no reports of abuse.

The Committee also noted that there had been no public submissions received in respect to the foreshadowed amendments or to the pre-February 2005 NDPSC meeting gazette notice.

DECISION 2005/44 - 1

In the interests of harmonisation with New Zealand, the Committee agreed to adopt the recommendations as foreshadowed at the June 2005 meeting to exempt sublingual tablets from scheduling.

Schedule 2 - Amendment

NICOTINE – amend entry to read:

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

Schedule 4 - Amendment

NICOTINE – amend entry to read:

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

(a) when included in Schedule 2;

(b) in chewing gum;

(c) in lozenges;

(d) for sublingual use; or

(e) in preparations for transdermal use.

Schedule 7 - Amendment

NICOTINE – amend entry to read:

NICOTINE **except**:

(a) when included in Schedule 2, 4 or 6;

(b) in chewing gum;

(c) in lozenges;

(d) for sublingual use;

(e) in preparations for transdermal use; or

(f) in tobacco prepared and packed for smoking.

1.8.1.3.3 HYOSCINE AND HYOSCYAMINE

PURPOSE

The Committee considered harmonising the cut-off to exempt concentrations in Appendix G for hyoscine and hyoscyamine in order to harmonise with New Zealand.

BACKGROUND

The NDPSC had previously considered a rationale which supported the maximum SUSDP listed Schedule 2 oral dose in one litre of preparation of 300 micrograms/L, to be an appropriate cut-off for atropine in Appendix G of the SUSDP.

However, the NDPSC also noted that the current cut-off's for atropine, hyoscine and hyoscyamine in Appendix G did not reflect the relative potencies of atropine and hyoscine and hyoscyamine. Members noted that Martindale reported hyoscyamine as

having twice the antimuscarinic potency of atropine and that hyoscine was a more powerful suppressant of salivation than atropine. Given the increased potency of hyoscyamine and hyoscine, the Committee based the cut-off's for these substances on a level that is half that of the cut-off for atropine or 150 micrograms/L.

The NDPSC agreed to amend the cut-off in Appendix G of the SUSDP for atropine to harmonise with New Zealand. However, it was agreed to amend the cut-off's for hyoscine and hyoscyamine to half that of atropine based on their increased toxicity relative to atropine. Consequently, harmonisation was not achieved for hyoscine and hyoscyamine.

However at the February 2005 meeting, the Committee agreed that the XXXXXXXX argument, namely that if atropine was at a concentration of 300 micrograms per litre, a child would need to consume a quantity in excess of 5 litres to reach the fatal dose of 1.6 mg, while an adult would need to consume considerably more, was also applicable to hyoscine and hyoscyamine and demonstrated a considerable safety margin that would allow the cut-off to exempt for hyoscine and hyoscyamine as outlined in Appendix G of the SUSDP to be amended to 300 micrograms.

The Committee agreed that on the basis of safety and to promote harmonisation with New Zealand, that the cut-off to exempt hyoscine and hyoscyamine as outlined in Appendix G of the SUSDP be amended to 300 micrograms. The Committee foreshadowed recommendations to this effect.

DISCUSSION

The Committee noted that there had been no public submissions received in response to the Gazettal of the foreshadowed amendments to the SUSDP in order to achieve harmonisation with New Zealand.

DECISION 2005/44 - 2

The Committee agreed that the cut-off to exempt for hyoscine and hyoscyamine as outlined in Appendix G of the SUSDP be amended to 300 micrograms in order to harmonise with New Zealand.

Appendix G - Amendment

HYOSCINE – amend entry to read:

HYOSCINE.	300 micrograms

HYOSCYAMINE – amend entry to read:

HYOSCYAMINE.	300 micrograms

1.8.1.3.4 CONSIDERATION OF SCHEDULING OF SUBSTANCES WHERE THERE ARE NO SCHEDULE 2 OR SCHEDULE 3 PRODUCTS IN THE MARKETPLACE

PURPOSE

The Committee considered foreshadowed amendments to certain substances in order to achieve scheduling harmonisation with New Zealand.

BACKGROUND

The February 2005 NDPSC meeting noted that the Trans-Tasman Harmonisation Working Party (TTHWP) had proposed a policy position that, where there were S2/S3 entries but no products included on the ARTG or on the New Zealand SMARTI, those scheduling entries should be deleted but the parent entry should be retained/added in Schedule 4 of the SUSDP.

The Committee recalled that the principles of harmonisation of scheduling of drugs and poisons established by the NCCTG stated in part, that the underlying principle was to harmonise on the least restrictive schedule while giving due consideration to public health and safety issues and/or specific jurisdictional needs. While the proposal by the TTHWP departed from these principles, it was only in relation to substances no longer marketed in either Australia or New Zealand.

The February 2005 NDPSC meeting was also advised that the TTHWP had recently been focusing on harmonisation in respect to Schedule 2 and 3 substances. In cooperation with New Zealand, the Working Party had identified numerous substances which were not registered in either or both Australia or New Zealand. The Working Party had therefore recommended to the NDPSC that these substances should not be deleted from the respective scheduling classification but that the most pragmatic way of dealing with the harmonisation of their scheduling was to place the parent drug in Schedule 4 and delete or amend as appropriate the corresponding Schedule 2 and/or Schedule 3 entries. It was also noted that most of the substances in question were old and had been historically assessed. By including them in Schedule 4, any future application for registration of a medicine containing those substances would necessitate an appropriate application to the registration authority accompanied by contemporary data in-keeping with current standards.

The NDPSC agreed that, given the large volume of harmonisation work yet to be completed, the Working Party's proposed approach for dealing with those substances no longer marketed presented a strategic solution that maintained the momentum towards harmonisation. However, the agreement of NCCTG to proceed in this way would be sought. Substances implicated in this decision and for which there were no S2 or S3 products marketed in Australia and New Zealand included butoconazole, butraconazole, carbuterol, clemastine, clemizole (S4 Australia), copaiba balsam, dichlorophen, dimethothiazine, diphenylpyraline, flunisolide, hexoprenaline, hydrargaphen (S4

Australia for internal use), jalap resin, mebhydrolin (S4 Australia), mequitazine, pentaerythritol tetranitrate, phenylpropanolamine, phenyltoloxamine, pomegranate and thenyldiamine.

The Committee was advised that New Zealand was also in agreement with this approach for older substances which were no longer marketed.

DISCUSSION

The Committee noted that at its 68th meeting, the NCCTG had endorsed the NDPSC's policy approach for dealing with substances identified by NDPSC and for which there were no S2 or S3 products marketed in Australia and New Zealand.

The proposed amendments had also been referred to New Zealand for comment before gazettal.

Public comment in response to the pre-meeting Gazette Notice was received from XXXXXXXX. XXXXXXXX did not support the removal of the substances from Schedule 2 and Schedule 3 unless there was evidence of safety concerns. In this regard XXXXXXXX did support the proposed scheduling amendments to phenylpropanolamine. XXXXXXXX noted that overall, the proposal was contrary to the principles of scheduling harmonisation established by the NCCTG. XXXXXXXX also noted that maintaining the current scheduling would not obviate the need to submit an appropriate application for evaluation by the regulatory authority which has responsibility for ensuring a product's safety, quality and efficacy in-keeping with current standards.

In considering XXXXXXXX's comments, the NDPSC recalled that the NCCTG had been advised of the departure from the harmonisation policy framework in this instance and had agreed with the NDPSC that it was appropriate.

With respect to mepyramine, the Committee noted that, while there were no products registered in Australia, there was one product, a 2% topical cream with a "Pharmacy Only' classification registered in New Zealand. The proposed amendment was to include mepyramine in Schedule 4 of the SUSDP. In respect to dermal use of products containing mepyramine, the Committee noted that this would be inconsistent with the NDPSC policy of not permitting the dermal use of sensitizing antihistamines. The Committee therefore agreed not to align the Schedule 2 classification of mepyramine with New Zealand. However, as there were no oral preparations of mepyramine registered in Australia, the Committee did recommend the deletion of mepyramine from Schedule 3 and the consequential amendment to Schedule 4.

In relation to the 'Pharmacy Only' (Schedule 2) classification of mepyramine in New Zealand, the Committee agreed that this should be referred to the New Zealand Medicines Classification Committee for consideration of its appropriateness and possible harmonisation of the New Zealand classification with the SUSDP having regard to concerns over the use of sensitizing antihistamines.

In relation to clemizole and mebhydrolin, the Committee agreed that there was no requirement to amend the existing Schedule 4 classification. In relation to hydrargaphen, the proposed Schedule 4 amendment to remove reference to internal use was also agreed. It was confirmed that there were no products containing clemizole, hydrargaphen or mebhydrolin available for use in either country.

The Committee agreed that these substances should be referred to New Zealand to consider harmonisation of scheduling with Australia.

DECISION 2005/44 - 3

Having regard to the absence in Australia and New Zealand of Schedule 2 and Schedule 3 products containing the following substances: butoconazole, butraconazole, carbuterol, clemastine, copaiba balsam, dichlorophen, dimethothiazine, diphenylpyraline, flunisolide, hexoprenaline, hydrargaphen, jalap resin, mequitazine, pentaerythritol tetranitrate, phenylpropanolamine, phenyltoloxamine, pomegranate and thenyldiamine, the Committee agreed to amend the scheduling of those substances in the interests of trans-Tasman harmonisation.

In respect to mepyramine, the Committee agreed to delete the Schedule 3 entry noting that there were no oral preparations containing mepyramine registered for use in Australia.

Schedule 2 - Amendments

DICHLOROPHEN – delete entry

DIPHENYLPYRALINE – delete entry

THENYLDIAMINE – delete entry

Schedule 3 – Amendments

CLEMASTINE – delete entry

DIPHENYLPYRALINE – delete entry

FLUNISOLIDE – delete entry

MEPYRAMINE – delete entry

PHENYLPROPANOLAMINE – delete entry

PHENYLTOLOXAMINE – delete entry

THENYLDIAMINE – delete entry

Schedule 4 – New entries

BUTOCONAZOLE.

BUTRACONAZOLE.

CARBUTEROL.

COPAIBA BALSAM.

DICHLOROPHEN for internal human therapeutic use.

DIMETHOTHIAZINE.

HEXOPRENALINE.

JALAP RESIN.

MEQUITAZINE.

PENTAERYTHRITOL TETRANITRATE.

POMEGRANATE (PUNICA GRANATUM) for human therapeutic use.

Schedule 4 - Amendments

CLEMASTINE – amend entry to read:

CLEMASTINE.

DIPHENYLPYRALINE – amend to read:

DIPHENYLPYRALINE.

FLUNISOLIDE – amend entry to read:

FLUNISOLIDE.

HYDRARGAPHEN – amend entry to read:

HYDRARGAPHEN.

MEPYRAMINE – amend entry to read:

MEPYRAMINE.

PHENYLPROPANOLAMINE – amend entry to read:

PHENYLPROPANOLAMINE.

PHENYLTOLOXAMINE – amend entry to read:

PHENYLTOLOXAMINE.

THENYLDIAMINE – amend entry to read:

THENYLDIAMINE.

Schedule 6 - Amendments

DICHLOROPHEN – amend entry to read:

DICHLOROPHEN **except**:

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

(b) in fabrics other than when:

(i) for human therapeutic use; or

(ii) as part of a registered pesticidal product.

1.8.1.3.5 CONSIDERATION OF SCHEDULING OF SUBSTANCES USED IN THE TREATMENT OF TINEA PEDIS

PURPOSE

The Committee considered the foreshadowed amendments to topical antifungals in the SUSDP in order to achieve scheduling harmonisation in scheduling with New Zealand.

BACKGROUND

The Committee had previously noted proposals from the TTHWP in relation to the harmonisation with New Zealand of scheduling for certain substances for the treatment of tinea pedis viz bifonazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole and tioconazole. In New Zealand, products containing these substances for the treatment of tinea pedis are exempt from scheduling.

The proposal to achieve scheduling harmonisation was therefore to amend the current Schedule 2 entries in the SUSDP to read “in preparations for dermal use except in preparations for the treatment of tinea pedis”. In the case of oxiconazole (for which there are no products for the treatment of tinea pedis registered in Australia), a Schedule 4 entry with exceptions was proposed.

The Committee requested that the Secretariat specifically seek comment from industry and professional bodies on the foreshadowed amendments. Comment was sought from XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX.

DISCUSSION

The Committee noted comments received from XXXXXXXX, XXXXXXXX and XXXXXXXX.

XXXXXXXX noted that:

- Topical antifungal treatments (for tinea pedis) generally require consumers to be dedicated to (once or twice) daily application of medication, good hygiene and appropriate selection of clothing and/or footwear for an extended period of time. Pharmacists are aware that this type of treatment regimen is regarded to be quite intensive by many consumers and often can be compromised resulting in less than optimal outcomes.
- Pharmacists are also aware that many consumers confuse fungal infections with other types of infections or skin conditions and often worsen or prolong the condition by selecting over-the-counter treatment which may not be appropriate.

For these reasons, XXXXXXXX felt that the proposed exemption of antifungals for the treatment of tinea pedis from scheduling was not desirable. XXXXXXXX further considered that while the substances may have a good safety profile, the general trend of how they are used indicated that open access was not a favourable scenario to achieve optimal and effective use.

In addition, XXXXXXXX had specific concerns with the proposed amendments applying to ketoconazole which they believed possessed certain characteristics which were different to other structurally related imidazoles. Though systemic absorption of ketoconazole from topical preparations had not been demonstrated, because ketoconazole was teratogenic, it was recommended that risk-benefit be discussed with a health professional before use during pregnancy. XXXXXXXX considered that the current S2 scheduling was highly desirable for ketoconazole and should be retained.

In response to the XXXXXXXX concerns in regard to the teratogenicity of ketoconazole, the Committee was advised that the TERIS database noted that a small risk could not be excluded, but a high risk of congenital abnormalities in the children of women treated topically with ketoconazole during pregnancy was unlikely.

In respect to ketoconazole and its teratogenic potential, MICROMEDEX noted that *high (toxic) doses of fluconazole, itraconazole, and ketoconazole have been reported to be teratogenic in rodents. Although there is little information about the use of these drugs in human pregnancy, there is a report of a woman who had received fluconazole 400 mg daily throughout pregnancy and who gave birth to an infant with severe craniofacial and*

limb abnormalities. The abnormalities resembled those associated with the Antley-Bixler syndrome, a genetic disorder, but a teratogenic effect could not be excluded. Although prescription-event-monitoring studies of fluconazole did not reveal adverse effects on the foetus, congenital abnormalities have occurred in infants whose mothers had received high doses of fluconazole for 3 months or more. Data collected by the manufacturer, relating to 198 women exposed to itraconazole during the first trimester of pregnancy, indicated that the malformation rate for both exposed women and matched controls was within the expected baseline risk for the general population. Nevertheless, the manufacturers recommend that fluconazole, itraconazole, and ketoconazole should be avoided during pregnancy.

Other azole antifungals including butoconazole, clotrimazole, econazole, miconazole, sulconazole, terconazole, and tioconazole are reported to be embryotoxic but not teratogenic in rodents given high doses. Many of these drugs are used topically or intravaginally and the systemic absorption from these routes of administration varies. While these drugs may not necessarily be contra-indicated in pregnancy, consideration should be given to these potential risks when choosing antifungal therapy for such patients.

The ADRAC had not received any reports of teratogenicity associated with ketoconazole. ADRAC had also noted that ketoconazole is classified as a pregnancy category B3 drug ie "drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans."

ADRAC also noted that ketoconazole was a potent cyp 3-4 inhibitor and had interactions with many drugs.

XXXXXXXX's comments were principally in respect to miconazole. They agreed with the proposal to amend the current Schedule 2 entry in the SUSDP as proposed.

XXXXXXXX noted that, as the proposals were in line with the NCCTG harmonization policy, they were acceptable to the industry.

DECISION 2005/44 - 4

The Committee agreed that in order to harmonise with New Zealand, the scheduling of bifonazole, clotrimazole, econazole, ketoconazole, miconazole, tioconazole and oxiconazole when used in the treatment of *tinea pedis* be amended as follows:

Schedule 2 - Amendments

BIFONAZOLE – amend entry to read:

BIFONAZOLE in preparations for dermal use **except**:

(a) in preparations containing 1 percent or less of bifonazole for the treatment of the scalp; or

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

CLOTRIMAZOLE – amend entry to read:

CLOTRIMAZOLE for human use in dermal preparations **except** in preparations for the treatment of tinea pedis.

ECONAZOLE – amend entry to read:

ECONAZOLE for human use in dermal preparations **except** in preparations for the treatment of tinea pedis.

KETOCONAZOLE – amend entry to read:

KETOCONAZOLE in preparations for dermal use **except**:

(a) in preparations containing 1 percent or less of ketoconazole for the treatment of the scalp; or

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

MICONAZOLE – amend entry to read:

MICONAZOLE for human use in dermal preparations **except** in preparations for the treatment of tinea pedis.

TIOCONAZOLE – amend entry to read:

TIOCONAZOLE in preparations for dermal use **except** in preparations for the treatment of tinea pedis.

Schedule 4 - Amendments

BIFONAZOLE – amend entry to read:

BIFONAZOLE **except**:

(a) when included in Schedule 2;

(b) in preparations for dermal use containing 1 percent or less of bifoconazole for the treatment of the scalp; or

(c) in preparations for dermal use for the treatment of tinea pedis.

CLOTRIMAZOLE – amend the entry to read:

CLOTRIMAZOLE **except**:

(a) when included in Schedules 2, 3 or 6; or

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

ECONAZOLE – amend the entry to read:

ECONAZOLE **except:**

(a) when included in Schedules 2, 3 or 6; or

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

KETOCONAZOLE – amend entry to read:

KETOCONAZOLE **except**:

(a) when included in Schedule 2;

(b) in preparations for dermal use containing 1 percent or less of ketoconazole for the treatment of the scalp; or

(c) in preparations for dermal use for the treatment of tinea pedis.

MICONAZOLE – amend the entry to read:

MICONAZOLE **except:**

(a) when included in Schedules 2, 3, or 6; or

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

OXICONAZOLE – amend entry to read:

OXICONAZOLE **except** in preparations for dermal use for the treatment of tinea pedis.

TIOCONAZOLE – amend to entry to read:

TIOCONAZOLE **except:**

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

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

1.8.1.3.6 CONSIDERATION OF AMENDMENTS TO SCHEDULING TO ACHIEVE HARMONISATION WITH NEW ZEALAND

PURPOSE

The Committee considered amendments to the scheduling of cimetidine, ethyl chloride, famotidine, nizatidine, prilocaine, ranitidine and silver sulfadiazine to achieve harmonisation with New Zealand.

BACKGROUND

H2 Antagonists - Cimetidine, Famotidine, Nizatidine, Ranitidine

The February 2005 NDPSC meeting noted advice from the TTHWP that the scheduling for cimetidine, famotidine, nizatidine and ranitidine was almost "essentially harmonised". In New Zealand, specific approval by the Minister or Director General was required to supply these substances as an S2 medicine. However, unlike the SUSDP entry, the New Zealand classification was not limited to "gastro-oesophageal reflux". The scope of the permitted indications was therefore different. To achieve scheduling harmonisation, the TTHWP proposed to the NDPSC that the SUSDP be amended by removing reference to the indication (which was considered a matter for the registration authority), and adding "when sold in the manufacturers original pack containing not more than 14 days' supply".

Prilocaine, Ethyl Chloride

The TTHWP had also proposed that, in order to achieve scheduling harmonisation for prilocaine, the NDPSC give consideration to deleting "topical use" and adding "dermal use" in line with the New Zealand classification. However, this would exclude eye drops which are covered by the terms "external use" or "topical use" in association with the descriptor "for ophthalmic use" or "for ocular use" or "in eye drops containing ……". As there are no eye drop medicines containing prilocaine on the ARTG, it was anticipated that this proposed amendment would not have product implications.

To align with New Zealand, the TTHWP had proposed that the Schedule 4 entry for ethyl chloride be amended by removing 'for inhalation anaesthesia". It was noted that New Zealand agreed to also make similar amendments in order to harmonise the scheduling of ethyl chloride.

Silver sulfadiazine

TTHWP had also considered the harmonisation of scheduling for silver sulfadiazine. The Working Party had sought comment from XXXXXXXX which noted the importance of the use of silver sulfadiazine for the treatment of minor burns. The Working Party's advice to NDPSC was that in the interests of harmonisation and in the absence of any public health concerns associated with a relaxation of scheduling to harmonise with New Zealand, the scheduling of silver sulfadiazine be aligned with that of New Zealand.

DISCUSSION

Comments on the foreshadowed amendments were received XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX.

H2 Antagonists - Cimetidine, Famotidine, Nizatidine, Ranitidine

XXXXXXXX did not have any objections to the proposal to remove reference to the indication in the SUSDP.

XXXXXXXX commented specifically in respect to ranitidine. In principle, XXXXXXXX had no objection to the proposed harmonisation of the ranitidine entries with New Zealand. XXXXXXXX did note however, that there were several schedule entries in the SUSDP that specified indications and questioned how the removal of reference to the indication for ranitidine would affect existing and future entries in the SUSDP. In response the Committee agreed that XXXXXXXX may have misunderstood the Committee's intention in relation to the removal of the indications. The Committee's proposal was solely in relation to the H2 antagonists and should not be read more broadly. The proposal assisted in ensuring that the Schedules in this case did not unnecessarily restrict use, consideration of which was the responsibility of the registration authority. The proposal would in fact, open the way for marketers of H2 antagonists in Australia to seek registration approval to modify their products to have a broader statement of use on the packaging. There was no intention by the Committee to review all entries in the SUSDP which included reference to indications.

XXXXXXXX noted that, as the proposals were in line with the NCCTG harmonization policy, they were acceptable to the industry.

Prilocaine, Ethyl chloride

Comment was only received from XXXXXXXX. XXXXXXXX noted that, as the proposals were in line with the NCCTG harmonization policy, they were acceptable to the industry.

In relation to ethyl chloride, the Committee confirmed that while there were industrial uses of ethyl chloride, there were no products for human therapeutic use in either Australia or New Zealand. The Committee therefore agreed to amend the Schedule 4

entry in the SUSDP to include "for human therapeutic use" thereby essentially harmonizing the scheduling with New Zealand.

Silver sulfadiazine

XXXXXXXX considered that the proposed inclusion of silver sulfadiazine in Schedule 2 of the SUSDP was not appropriate.

Specifically, XXXXXXXX commented that:

- The absorption of SSD can vary depending on the surface area to which it is applied and extent of tissue damage. When used topically over extensive areas, serum concentrations may approach therapeutic concentrations.

- Patients sensitive to other sulfonamides, frusemide, thiazide diuretics, sulfonylureas or carbonic anhydrase inhibitors may also be sensitive to SSD.

- Clinical significant interactions or related problems are also likely with the concurrent use of SSD and proteolytic enzymes such as collagenase and papain.

- SSD cream generally has little place in outpatient minor burn wound management, although its application frequency has a soothing effect on acute burns.

- SSD is a broad spectrum antibacterial and antifungal agent and is used for prophylaxis and treatment of indications other than burns such as pressure sores and dermal ulcers. With greater accessibility to consumers in the community, development of resistance over time is of concern. This concern is reflected in current policies of many hospitals where the use of silver sulfadiazine is highly restricted.

- As inclusion in Schedule 2 would permit advertising to the public, PSA believed that this would lead to greater demand and expectations of consumers, and overall result in higher levels of inappropriate use with the associated risk of resistance developing in community pathogens.

XXXXXXXX noted that, as the proposals were in line with the NCCTG harmonization policy, they were acceptable to the industry.

XXXXXXXX did not support the proposals to amend the scheduling of silver sulfadiazine to achieve harmonisation with New Zealand.

XXXXXXXX commented that the down-scheduling of silver sulfadiazine was previously considered at the 37th meeting of the NDPSC in February 2003. At that time it was not considered appropriate due to the potential problem of resistance. Recent, informal communications with Infectious Diseases experts indicate that they still consider this to

be an important issue and would not support the wider availability of silver sulfadiazine. Silver sulfadiazine has traditionally been used for full thickness burns and not minor burns, so widening of its availability may not be appropriate. For example, at Royal Perth Hospital, silver sulfadiazine cream is currently restricted for full thickness skin loss in burns or plastics unit or microbiology/infectious diseases approval only.

In addition, XXXXXXXX noted that there had been some reports of delayed wound healing, which would make the use of silver sulfadiazine inappropriate, except under medical supervision.

When applied to large open wounds or burns, XXXXXXXX considered that silver sulfadiazine may be absorbed into the blood stream with the potential to cause leucopenia and interact with a number of medications including anti-diabetic medications and phenytoin. There are a number of contraindications to silver sulfadiazine that also mandate medical supervision of its use. It should not be used on heavily exudative wounds, by patients allergic to sulpha drugs, or by those with decreased liver or kidney function. Although the incidence of these problems may be low, they may be serious and still have to be considered. It was the opinion of XXXXXXXX that experts in the area of burn and wound management and infectious disease should be formally consulted to gauge scientific opinion about the appropriateness of the change.

Having regard to the comments received, the Committee agreed not to proceed with the foreshadowed harmonisation proposal and to retain the current scheduling for silver sulfadiazine. The Secretariat was requested to write to New Zealand advising of the decision not to proceed with harmonisation.

DECISION 2005/44 - 5

The Committee agreed to the foreshadowed amendments to the scheduling of the H2 antagonists, (cimetidine, famotidine, nizatidine and ranitidine) and also the scheduling for prilocaine and ethyl chloride to harmonise with New Zealand. The Committee did not agree to amend the scheduling for silver sulfadiazine.

Schedule 2 - Amendments

FAMOTIDINE – amend entry to read:

FAMOTIDINE when sold in the manufacturer's original pack containing not more than 14 days supply.

NIZATIDINE – amend entry to read:

NIZATIDINE when sold in the manufacturer's original pack containing not more than 14 days supply.

PRILOCAINE – amend entry to read:

PRILOCAINE in preparations for dermal use containing 10 per cent or less of total local anaesthetic substances.

RANITIDINE – amend entry to read:

RANITIDINE when sold in the manufacturer's original pack containing not more than 14 days supply.

Schedule 3 – Amendments

CIMETIDINE – amend entry to read:

CIMETIDINE when sold in the manufacturer's original pack containing not more than 14 days supply.

Schedule 4 - Amendments

ETHYL CHLORIDE – amend entry to read:

ETHYL CHLORIDE for human therapeutic use.

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

2.1 SUSDP, PART 1

2.1.1 INTERPRETATION – "DERMAL USE", "TOPICAL USE" AND "EXTERNAL"

PURPOSE

The Committee considered the interpretation of "Dermal Use", "Topical Use" and "External" as applied to substances for use on nails.

BACKGROUND

XXXXXXXX sought advice from the Secretariat prior to the February 2005 meeting regarding the expected scheduling status of a proposed product containing up to XXX% XXXXXXXX when applied to the nails for the treatment of fungal infections. The primary entry for XXXXXXXX was in Schedule 4 of the SUSDP, with an entry in Schedule 2 when in preparations for dermal use. XXXXXXXX sought clarification as to whether its product would fall under the definition in the SUSDP for "dermal use".

The Secretariat subsequently sought advice from jurisdictional members on whether the nail product would fall under the Schedule 2 XXXXXXXX entry. Members recognised the need to review the definitions in the SUSDP for "Dermal Use", "External" and "Topical Use" as they apply to nail products and agreed to refer the matter for consideration at the February 2005 NDPSC Meeting. The current SUSDP definitions are:

- "**Dermal use**" means application to the skin primarily for localised effect.
- "**External**" in relation to the use of a poison means application in the ears, eyes or nose or to a body surface other than in the mouth, rectum, vagina, urethra or other body orifice.
- "**Topical use**" means application of a poison for the purpose of producing a localised effect on the surface of the organ or within the tissue to which it is applied.

At the February 2005 meeting the Committee concurred with the views expressed by the majority of the jurisdictional members prior to the meeting in that, functionally, nails are distinct from skin and have different characteristics. To this end Members agreed that there was a need to provide clarity to stakeholders in terms of which SUSDP definition covers those substances for application to the nail. The Committee considered possible options including a specific definition for "nail" in the SUSDP, the use of the statement "application to nail only" in the relevant Schedule entries or including concentration cut-offs based on the substance's toxicological profile for those Schedule entries that allow application to nails.

The Committee also noted that the New Zealand definitions were harmonised with the SUSDP, with no specific reference to nails.

The Members agreed that additional information and consultation with stakeholders was required before the Committee could further consider this issue to ensure that there would be no unintended regulatory impact on products while creating a consistent approach to scheduling products for the treatment of nails.

DISCUSSION

The Committee considered two submissions from XXXXXXXX regarding its recent application to the Over-the-Counter (OTC) Medicines Section, TGA, to introduce several changes to the Product Information and label for XXXXXXXX, an antifungal treatment tincture for fungal nail infections containing the active miconazole. The Committee noted the OTC Section's response that XXXXXXXX should be classified as a Schedule 4 product, citing the current definition in the SUSDP of "dermal".

The Committee considered XXXXXXXX's request that members consider two options:

- Amend the miconazole entry to read "for human use in dermal preparations including fingernails and toenails; or

- Amend the definition of dermal to include fingernails and toenails as well as the skin.

The Members were further advised that the OTC Section noted that while the Schedule 2 entry for miconazole includes dermal, this entry has been there for a long time and, at the time of the entry, there was no definition of "dermal use". The OTC Section further noted that as "dermal use" refers to skin with no reference to nails, products such as XXXXXXXX are captured by Schedule 4, an outcome which appeared unintended. The OTC Section indicated that the problem seemed to be the use of "dermal" in the SUSDP entries. The OTC Section also indicated that problems such as with XXXXXXXX would be covered if the SUSDP entry were to be changed from "dermal" to "topical" or "external".

The Committee agreed that one option to resolve the miconazole issue was to amend the Schedule 2 entry for miconazole to explicitly allow application to nail.

The Committee noted separate advice from OTC Section which identified a range of Schedule 2 antifungals whose entries included the word dermal and could potentially be associated with nail products open to inadvertent Schedule 4 capture. The Committee was also advised of the results of an Australian Register of Therapeutic Goods (ARTG) search for all products containing the substances identified by the OTC Section. This search also captured products not for use on nails but which may be affected by any scheduling changes.

Members were further advised that a separate search by the Secretariat for all ARTG entries containing "nail" returned 219 current products. However, this included non-relevant items such as surgical nails for bones and oral vitamin supplements with claims for improving the appearance of hair and nails.

The Committee agreed that while these methods have not exhaustively identified all products for use on nails it has indicated that many Schedule 2 substances for nails currently have a dermal definition and a decision that nails are not dermal could revert many of these products to Schedule 4.

The Committee discussed the following arguments against considering nail to be dermal:

- A member noted that for infections of the nail, often deep within the tissue, there was a need for quite different treatment than would normally be used for skin infections. It was further noted that pharmacokinetically there was quite a difference between skin and nail.
- A member noted that there would be a risk of inadvertently allowing a number of potential nail products to be in Schedule 2 when the Committee had not considered the application to nail use pattern when creating the Schedule 2 entry for these substances. The member further argued that these concerns extended to the implication of efficacy which may then be associated with such products.

- Some products on the market, such as XXXXXXXX (a ketoconazole cream), specifically indicates not for infections involving nail – implying that some manufacturers view nail and skin as distinct.
- A member further noted that if nails are included in the dermal definition then this in effect robs the Committee of a definition for skin only.

The Committee, in addition to the above arguments, noted the following for considering nail to be topical:

- Nails implicitly come under the current external and topical use definitions.
- Topical would make a better fit given the use pattern is usually penetration within the nail i.e. within the tissue to which it is applied.

As a consequence of the above arguments a member proposed to amend the definition of topical to include nail.

The Committee then discussed the alternative – to consider broadening the definition of dermal to include nail – and noted the following:

- That changing a Schedule entry from dermal to topical or external may imply that the poison can be applied to the ears, eyes or nose etc. which may not be appropriate. This approach would also require amendments to many Schedule 2 entries. The members were advised that adding a specific reference to nail in an individual entry would also require amendments to many Schedule 2 entries.
- The Committee noted that many of the current dermal entries are harmonised with New Zealand and that there appears to be an implication that nail products in New Zealand are currently considered to be dermal products by industry.
- The Committee noted that the OTC Section's interpretation that products such as XXXXXXXX are captured by Schedule 4 does not appear to have been widely disseminated to manufacturers who still largely appear to consider their nail products as dermal.
- A member noted that concerns over high strength dermal products would be addressed by the registration processes. In response to some of the Committee's concerns, it was also noted that the registration process assesses efficacy.
- A member asserted that if dermal does not include nail there would be further confusion caused by the issue of defining what "around the nail" would mean.

As a consequence of these arguments a member proposed to foreshadow an amendment to the definition of dermal to include nail.

The Committee agreed that additional consultation with stakeholders was required before the Committee could further consider this issue. The Committee also agreed that there was a need to draw this issue to the attention of the Therapeutics Policy and Planning

Committee (TPPC) as there are currently none of these definitions in the *Therapeutic Goods Act* and that the SUSDP's definitions may, by default, become the TGA's definitions once the trans-Tasman Joint Agency is established.

OUTCOME

The Committee agreed to gazette the Committee's intent to review the definition of dermal in relation to application to nail as this will provide stakeholders with an opportunity to comment on any possible ramifications. The Committee also agreed for clarity to foreshadow an amendment to the Schedule 2 miconazole entry to allow application to nail in the absence of any public health concerns. The foreshadowed amendment also reflects the outcome of item 1.8.1.3.5 – consideration of scheduling of substances used in the treatment of tinea pedis.

FORESHADOWED DECISION (for consideration at the October 2005 meeting)

Schedule 2 - Amendment

MICONAZOLE – Amend to read:

MICONAZOLE for human use in dermal preparations and for application to the nails **except** in preparations for the treatment of tinea pedis.

2.1.2 DEFINITION OF 'CHILD RESISTANCE' AND STORAGE STATEMENTS FOR SCHEDULE 5 AND SCHEDULE 6 PRODUCTS

PURPOSE

The Committee considered:

- the definition of child-resistance in the SUSDP with regard to products that meet the definition of "non-access packaging".
- the inclusion of a general statement addressing the requirements for storage of Schedule 5 and 6 poisons in Part 3 of the SUSDP.

BACKGROUND

At the October 2003 NDPSC meeting the Committee decided that the definition of child-resistant closure/packaging in the SUSDP was too narrow for the purposes of poisons regulation and did not account for packaging and closures which were sufficient to render their contents inaccessible to children but would fail to meet the strict definition of "child-resistant packaging" (CRP) or "child-resistant closure" (CRC) according to AS1928-2001 (the Australian Standard used as one of the base standards in the SUSDP

definitions for CRC and CRP). A submission from XXXXXXXX advised that XXXXXXXX believed that the definition of a CRC in the SUSDP was limited and restrictive in that it did not include products which were intended for single use. XXXXXXXX supported the inclusion of AS4710-2001 in the SUSDP as a suitable standard for assessing the compliance of CRCs on single-use packaging.

At the February 2004 NDPSC meeting the Committee considered the inclusion of AS4710-2001 in the definition of CRP but agreed that it was inappropriate on the grounds that AS4710-2001 tests for packaging that was designed not to be opened. The Committee also noted arguments for keeping AS4710-2001 separate from "child-resistant packaging" by XXXXXXXX. Counter arguments were put forward by XXXXXXXX who noted that AS4710 was modelled and derived from AS1928, that AS4710 had an implied definition of child resistance and that the terms "non-access" and "child resistance" are in effect synonymous.

At the June 2004 NDPSC meeting the Committee agreed to replace the definitions for CRC and CRP with the current definitions and included the current definition for "non-access packaging" in the SUSDP based on AS4710-2001. XXXXXXXX submitted a post-meeting comment which addressed issues including that:

- products which only comply with AS4710-2001 cannot claim to be "child-resistant" despite AS4710 and AS1928 being essentially similar Standards with similar aims.
- there are significant differences between the States and Territories in their legislation with regard to CRC and CRP resulting in a burden to industry. XXXXXXXX urged the Committee to work towards national criteria so that acceptance of a CRC or CRP in one jurisdiction results in acceptance in every other jurisdiction. The Committee agreed to refer XXXXXXXX's comments on this issue to NCCTG (see Item 1.7.1.5). Additionally, XXXXXXXX pointed out that there are differences between the Jurisdictions in the requirements for retail storage of Schedule 5 (and Schedule 6) poisons. The Committee agreed that this matter should be referred to XXXXXXXX with a view to the development of uniform approach to the storage of these substances.

DISCUSSION

The members noted that AS1928-2001 "child-resistant packages" specifies the requirements for reclosable and non-closable packages which are defined as:

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

The members also noted that AS4710-2001 "packages for chemicals not intended for access or contact with their contents by humans" specifies requirements for non-access and non-contact packages which are defined as:

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

The Committee was advised of a request from XXXXXXXX, a XXXXXXXX, regarding the definition of "child-resistance" in the SUSDP.

The Committee considered XXXXXXXX's request that the Committee provide advice on the issue of child resistance for devices and products such as cockroach baits which comply with the definition of "non-access packaging" but do not comply with AS1928-2001. XXXXXXXX argued that this situation made it impossible for such devices and products to comply with the current definition of child-resistance in the SUSDP. He also wished to draw the Committee's attention to his previous comments on the issue of CRCs and CRP and indicated that products such as cockroach baits were the reason why he recommended to Standards Australia to create AS4710-2001.

The members were advised that XXXXXXXX's client was the manufacturer of cockroach baits with an active ingredient (5g/kg chlorpyrifos) which was a Schedule 5 poison. XXXXXXXX noted that in some Australian jurisdictions (South Australia was used for this example) his client's cockroach baits (and similar products) must be stored at the retail store at a height of not less than 1.2 metres above the floor level because it was not:

- enclosed in a child-resistant package approved by the Minister;
- enclosed in a blister pack; or
- stored in a container that has a capacity of not less than 5 litres or a gross weight of not less than 5 kilograms.

The Committee was further advised that XXXXXXXX's client was requesting to have their packaging approved as "child-resistant" as defined in the SUSDP. The Committee noted, however, that the cage of the cockroach bait was not reclosable or reusable and its contents are not intended for access by humans. XXXXXXXX's submission advised:

- that to comply with the definition of child-resistance contained within the SUSDP only AS1928-2001 was really applicable.
- because it is a single-use non-reclosable package Section 2 of AS1928-2001 was not applicable.
- Section 3 ("Requirements for non-reclosable packages") of AS1928-2001 cannot be used because in essence the criteria in this section of the Standard is test of seal

strength and as the cockroach baits have open "windows" to allow the cockroaches to reach the poison they cannot be regarded as "sealed" and therefore the "Test for Integrity of Seal" cannot be used.

- hence it is impossible for such devices and products to comply with the current definition of child-resistance as contained in the SUSDP.

The Committee also noted that XXXXXXXX had responded regarding the requirements for retail storage of Schedule 5 and 6 poisons and the need for a uniform approach to this matter. The members were advised that XXXXXXXX discussed this subject XXXXXXXX and had recommended to the Committee inclusion of a paragraph in Part 3 of the SUSDP under the Storage heading. XXXXXXXX had suggested the following wording:

> "A person who sells or supplies a Schedule 5 or Schedule 6 poison in a retail shop must keep those poisons in such a way that, when displayed for sale, they are positioned at least 1.2 metres above the floor except when-
>
> - Packed in a container fitted with a child-resistant closure.
> - In a container with a capacity of 5 litres/5 kilograms or more.
> - Packed in child-resistant packaging.
> - A hair dye packed with a volume of 50 millilitres or less.
>
> They should be displayed in such a way to prevent contamination of human or animal food, or beverages should a leak or breakage occur."

XXXXXXXX also advised the Committee that should this proposition be accepted States and Territories have the option to include it by adoption into their relevant Poisons legislation, thus enhancing national consistency. XXXXXXXX thought it would give a clear message to retailers as to the minimum standard that is acceptable for storage of these substances.

The Committee considered that adding an additional exception "Packed in non-access packaging" to XXXXXXXX's recommendation would resolve the issue where some Schedule 5 and 6 storage regulations do not appear to account for packaging which is sufficient to render their contents inaccessible to children but are not CRP or CRC. The Committee generally agreed that this additional exception also addresses many of XXXXXXXX's concerns.

The Committee was further advised that submissions were also received from XXXXXXXX, XXXXXXXX and XXXXXXXX which indicated an interest in products that require compliance with child resistance packaging.

DECISION 2005/44 - 6

The Committee agreed to the XXXXXXXX recommendation to include a paragraph in Part 3 of the SUSDP under the storage heading referring to the storage of Schedule 5 and 6 poisons to enhance national consistency. The Committee also agreed that an additional exception be added to XXXXXXXX's recommendation to reflect the existence of the definition for "Non-access Packaging" in the SUSDP.

Part 3 – Storage – New entry

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

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

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

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 ALKALINE SALTS

PURPOSE

The Committee considered Poison Information Centre (PIC) responses concerning exposures involving alkaline salts.

BACKGROUND

The February 2004 meeting considered a review of alkaline salts by XXXXXXXX. The review addressed issues including the cut-off pH for scheduling, total alkalinity, the concentration at which the pH of a product should be measured, and the greater accessibility of automatic dishwasher detergents compared with laundry detergents in the home. Among the review's proposals was changing the cut-off pH for inclusion in Schedule 5 to "more than 11.0". Members 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 report. Accordingly, the Committee asked that more information be obtained by XXXXXXXX on the international control of similar substances.

At the June 2004 meeting the Committee noted a XXXXXXXX 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 XXXXXXXX Member determine the number of products currently on the Australian market with a pH between 11 and 11.5 and that the XXXXXXXX and XXXXXXXX Members seek from their respective PICs information regarding the number of poisonings attributed to these products and the identity of the products involved.

At the October 2004 meeting, the Committee noted information regarding poisonings involving alkaline detergents from the XXXXXXXX PIC. The XXXXXXXX PIC services XXXXXXXX. The Committee noted that the data collected by the XXXXXXXX PIC did not include any outcome data, either in terms of evolving symptomatology, adverse sequele or subsequent hospitalisation or other medical treatment. The Committee noted that this was 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.

Members also 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. The Committee agreed the current scheduling of alkaline salts remained appropriate. The Committee further agreed that the Secretariat should investigate the possibility of prospective data collection specifically based around alkaline salts (as defined in the SUSDP) with the State and Territory PICs.

DISCUSSION

The Committee was advised that information was received from the XXXXXXXX, XXXXXXXX and XXXXXXXX PICs in response to a request from the Secretariat for the PICs to collect the following information, over a three month period:

- The numbers of exposures to laundry detergents and automatic dishwasher detergents;
- The product name and brand;
- The formulation (i.e. liquid, tablet or powder);
- Age of the person exposed;
- Route of exposure; and
- Whether the person was referred to a hospital or GP.

The Committee particularly noted the following from the PIC responses:

XXXXXXXX – for the 3 months from February to April 2005

- Laundry detergents – 45 exposures, 2 referred to a doctor or hospital. Treatment was discussed with a doctor or registered nurse in 5 exposures.
- Liquid dishwater detergents – 2 exposures, both referred to doctor or hospital.
- Tablet dishwater detergents – 16 exposures, 2 referred to doctor or hospital. Treatment discussed with doctor in 2 exposures.
- Powder/granule dishwasher detergents – 26 exposures, 6 referred to a doctor or hospital. In 15 exposures the source was sludge/residue after the dishwater cycle.

XXXXXXXX – for the 3 months from 10 January to 10 April 2005

- Automatic dishwater detergents – 66 exposures, 20 referred to a doctor or hospital.
- Laundry detergents – 45 exposures, 2 referred to a doctor or hospital. Treatment was discussed with a doctor or registered nurse in 5 exposures.

XXXXXXXX – for the 3 months 1 March to 1 June 2005

- Automatic dishwater detergents – 107 exposures, 15 referred to a doctor or hospital.
- Laundry detergents – 146 exposures, 28 referred to a doctor or hospital.

The Committee generally agreed that while the information from the PICs was useful, there was still a lack of outcome data. The Members also noted that the information from the PICs did not characterise products that caused a poisoning into those with a pH below 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.

A member noted that, in looking at the PIC data, XXXXXXXX appeared to be highly represented. The member suggested that the Committee may wish to consider if this was just a reflection of market share or if there packaging issues that make this product attractive to children and infants.

A member also noted, in discussions regarding the pH cut-offs for the alkaline salt scheduling, that the potential harm was not just a simple correlation to pH. Issues such as alkaline reserve and buffer capacity needed to be taken into account and there was no really useful test that can predict the corrosivity of these alkaline salt products. The member thus questioned the usefulness of distinguishing between pH 11 and pH 11.5 as recommended by the XXXXXXXX review of alkaline salts.

The Committee also noted the following from public submissions to the October 2004 NDPSC meeting:

- Some 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.
- A company indicated 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.
- That a change to the scheduling of alkaline salts would have an impact to labelling, packaging, and presentation.

A member advised the meeting of an incident in Queensland late in 2005 where an 18 month infant ingested some XXXXXXXX granular dishwashing detergent with a pH of 13.5. The infant was admitted to hospital where doctors subsequently advised that the child was likely to never be able to eat or drink normally. The product was fitted with a cap that resembled a Child-resistant Closure (CRC) but, perhaps because a CRC was not legally required, it appeared that the cap was not, in fact, a CRC.

A member also advised the Committee that Safekids New Zealand have released a position paper on dishwashing powder (Caustic Poison in Our Kitchens – January 2005) which stated there were 615 incidents in New Zealand between June 2003 and January 2005 with 15 admissions to hospital. It was also indicated that New Zealand would be bringing in regulations, probably in 2006, where there will be mandatory CRC's on all alkaline salt dishwashing products.

A member suggested that the Committee should consider the CRC requirements for alkaline salt dishwashing products in the SUSDP. In particular, the member advocated that there was a need to consider requiring all dishwashing products containing alkaline salts to be fitted with CRCs. This could perhaps be achieved by:

- requiring dishwashing products containing alkaline salts to have a CRC before qualifying for the current Schedule 5 exemption; and
- by expanding the current CRC requirements as set out in Part 2 of the SUSDP for alkaline salts labelled for use in dishwashers to include all forms, not just tablets, liquids or gels. This suggestion was particularly targeted at improving the safety of dishwasher products using alkaline salts in powder form.

The XXXXXXXX representative advised that XXXXXXXX and XXXXXXXX are likely to be making a submission to the October 2005 NDPSC meeting regarding the need to require CRCs on all dishwashing products containing alkaline salts.

A member noted that an added challenge of the dishwasher alkaline salts is that frequently children access the slurry/residue left in the dishwasher after use, an exposure route that would fail to be address by any CRC change. The member suggested that the Committee should also look at the labelling, as well as the CRC requirements, to see if the labels really convey that these products can potentially be very toxic to children. The member asserted that if parents are effectively reached with this message then this may work to dispel the complacency that allows children to access containers under sinks and product or residue in open dishwashers.

The Committee agreed that there was currently insufficient information to justify a change in the scheduling of alkaline salts at this time. The Committee also agreed to gazette for the October 2005 NDPSC meeting a consideration of scheduling of alkaline salts including CRC and labelling requirements for dishwasher products.

The Committee also agreed that there was a need to obtain further information regarding outcomes of alkaline salt poisonings, noting that the PICs are not set up to collect

outcome data. A member suggested that the Secretariat approach XXXXXXXX regarding XXXXXXXX's capacity to contribute information on alkaline salt poisonings and whether alkaline salt poisonings are currently monitored by XXXXXXXX. Additionally, some jurisdictional members indicated the possibility of providing hospital separation data on alkaline salt poisonings for consideration at the October 2005 NDPSC meeting.

The XXXXXXXX representative also undertook to approach the manufactures of the products mentioned in the PIC data seeking information on the pH strengths and market share of these products. The Committee generally agreed that this information would also give some indication about whether particular products are over represented in the PIC data or whether this just reflects market share.

OUTCOME

The Committee noted the information received from the Poisons Information Centres and agreed that the current scheduling of alkaline salts remains appropriate at this stage. The Committee further agreed to consider the requirements for Child-resistant Closures and labelling of dishwasher products containing alkaline salts at the October 2005 NDPSC meeting.

4.2 THIABENDAZOLE

PURPOSE

The Committee considered the scheduling of thiabendazole.

BACKGROUND

XXXXXXXX submitted an application for the registration of a new product, XXXXXXXX, containing XXX% thiabendazole. The product was intended for fungicidal and acaricidal treatment of XXXXXXXX.

At the November 1974 NDPSC meeting, thiabendazole was exempted from the requirements of scheduling. At the November 1996 meeting, the Committee moved thiabendazole from Appendix B and included it in Schedule 5 for the treatment of animals, on the basis of embryotoxicity and foetotoxicity in mice, rats and rabbits. Thiabendazole for human therapeutic use was included in Schedule 2 at the May 2000 meeting on the recommendation of the Trans-Tasman Harmonisation Working Party.

At the February 2005 NDPSC meeting the Committee considered amending the Schedule 5 entry to include use as a fungicide on the basis of the toxicity profile for thiabendazole. The Committee's attention was drawn to the existence of two currently unscheduled products containing 50% thiabendazole. A member questioned the necessity of amending the current Schedule 5 entry to include fungicidal use given the apparent

history of safe use of the 50% thiabendazole products and the likely regulatory impact resulting from any amendment to the entry. The XXXXXXXX member advised the Committee that both of the 50% thiabendazole products were used as crop fungicides and proposed a cut-off of 50% to minimise the regulatory impact.

The members generally agreed that, given the limited human exposure of the proposed use and the low toxicity exhibited by the substance, an entry in Schedule 5 with a cut-off of 25% exemption from the requirements of scheduling was appropriate. However, the Committee agreed to defer consideration to allow data for the two unscheduled 50% thiabendazole fungicides to be obtained.

The applicant, XXXXXXXX, was informed that the Committee did not intend to schedule their product containing XXX% or less thiabendazole, but that the Committee wished to, before finalising the scheduling, review some other products in this class that have higher thiabendazole content.

The Secretariat was asked to seek data from the APVMA for the two unscheduled 50% thiabendazole fungicides, XXXXXXXX and XXXXXXXX, for the June 2005 NDPSC meeting.

DISCUSSION

The Committee noted the following points considered at the February 2005 NDPSC meeting:

- In the Office of Chemical Safety (OCS) evaluation report XXXXXXXX had [rest of sentence deleted].
- On the basis of its toxicity profile the OCS recommended that the current Schedule 5 entry for thiabendazole be amended to include use as a fungicide. Due to the low oral and dermal toxicity of thiabendazole, the lack of eye or skin irritant activity and the low potential inhalation hazard, the OCS report also recommended an exemption from the requirements of Scheduling for products containing 25% or less of thiabendazole.
- A search of the PUBCRIS Database found six agricultural and veterinary chemicals registered with the APVMA containing thiabendazole. Of these, one was labelled as Schedule 5 (88% thiabendazole w/w), one as Schedule 6 (20% w/v; containing thiram 36% w/v) and one as Schedule 4 (4% w/w; containing dexamethasone 0.9% w/w). The remaining three were identified as unscheduled products (one at 17.6% w/v and two at 50% w/v).

The Committee was advised that [remainder sentence deleted].

The Committee noted that APVMA had approached the registrants for the two unscheduled 50% thiabendazole fungicides, XXXXXXXX and XXXXXXXX. The registrants were asked if they had any data relevant to the consideration of the scheduling

of thiabendazole. XXXXXXXX advised APVMA that they do not have any data. XXXXXXXX indicated to APVMA that Schedule 5 was acceptable to them. XXXXXXXX also made a submission to the Committee.

The members were advised that XXXXXXXX formulates, markets and sells a 500 g/L thiabendazole preparation for use in controlling XXXXXXXX. The Committee noted that XXXXXXXX supported a cut-off for scheduling of thiabendazole for agricultural chemical use of 50% (500 g/L).

The Committee particularly noted the following from the information supplied by XXXXXXXX on its 50% thiabendazole product:

- The product had [remainder of sentence deleted].
- A copy of the European MSDS for the product indicated that [remainder of sentence deleted].

The Committee considered that, while noting that the OCS had been unable to make a recommendation regarding a 50% exemption for thiabendazole from Schedule 5, there was no data to justify a 25% rather than 50% cut-off. Additionally, the low oral and dermal toxicity of the 50% thiabendazole product, together with the lack of eye or skin irritant activity and the low potential inhalation hazard, was consistent with being exempt from the requirements of scheduling.

DECISION 2005/44 - 7

The Committee agreed to amend the entry for thiabendazole in Schedule 5 to include use as a fungicide and to exempt such products containing thiabendazole at 50 % or less when used as a fungicide from the requirements of scheduling on the basis of low toxicity.

Schedule 5 - Amendment

THIABENDAZOLE – Amend entry to read:

THIABENDAZOLE:

(a) for the treatment of animals; or

(b) when packed and labelled for use as a fungicide **except** in preparations containing 50 per cent or less of thiabendazole.

4.3 EYELASH AND EYEBROW TINTING PRODUCTS

PURPOSE

The Committee considered:

- amending the entries for phenylenediamines and toluenediamines in Schedule 6 to allow the use of appropriately labelled eyebrow and eyelash tinting products containing these substances in the home and/or in salons; and
- inclusion in Appendix C of preparations containing phenylenediamines and toluenediamines for eyebrow and eyelash tinting which would not be covered by the Schedule 6 entry.

BACKGROUND

At the February and June 2004 NDPSC meetings the Committee considered the outcomes of investigations into incorrectly packed and labelled eyelash and eyebrow tinting and hair care products containing paraphenylenediamine and toluenediamine.

The Committee was advised that XXXXXXXX had investigated claims of the retail sale of several hair dye products not labelled with the required warnings – "This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye"; or as a Schedule 6 poison.

The Committee was also advised that XXXXXXXX had informed companies that, until the labelling of eyelash and eyebrow tinting products issue was resolved, XXXXXXXX would only allow salon use of these products. It was indicated that for 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.

At the October 2004 NDPSC meeting the Committee noted the outcomes of the NICNAS preliminary review of chemicals in hair dyes and the NICNAS report on skin and eye irritancy for paraphenylenediamine and toluenediamine. Based on the outcomes of the report on skin and eye irritancy, 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 taken due to concerns surrounding the potential of the chemicals to cause severe eye injuries.

At the February 2005 NDPSC meeting the Committee agreed to foreshadow two options; (1) an amendment to the Schedule 6 entry to allow the use of appropriately labelled eyelash and eyebrow tinting products in salons only; and (2) consideration of a similar amendment which would allow home use of such products. Furthermore, the Committee

agreed to vary the foreshadowed Appendix C entries and foreshadow the inclusion in Appendix C of other preparations containing phenylenediamines and toluenediamines for eyebrow and eyelash tinting which would not be covered by the Schedule 6 entry.

The Committee agreed to take this approach on the grounds that the potential hazard posed by such products when used in homes or salons could be minimised through appropriate labelling which should also address the potential for hair-dye products to be used inappropriately for eyelash and eyebrow tinting should eyelash and eyebrow tinting products containing phenylenediamine and toluenediamine be placed in Appendix C. Furthermore, members agreed to seek expert advice from XXXXXXXX.

DISCUSSION

The Committee was advised that a response had been received from XXXXXXXX which advised that both dyes are known to be associated with quite severe reactions and sensitisation and that this parallels the clinical experience of the adviser. The members noted the XXXXXXXX conclusion that there would seem to be a case for reviewing if not banning their use. XXXXXXXX also provided relevant sections from *Toxicology of the Eye* for the information of the Committee.

Members were advised that the Foreshadowed Decision in the record of reasons from the February 2005 NDPSC meeting contained an error which was detected by a member and XXXXXXXX. This error would have excluded eyelash and eyebrow products from Schedule 6 and hence be captured by the Appendix C entries.

The Committee noted that a submission had been received from XXXXXXXX, on behalf of XXXXXXXX, setting out its case that eyebrow and eyelash tinting products containing phenylenediamine and toluenediamine can be safely used in the home. The members noted that the submission supported the foreshadowed decision which would allow the use of these products in the salon and the home. The Committee particularly noted the following data from the submission:

- These products are commonly sold in the EU and the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) in 2002 concluded that 2.5% aqueous phenylenediamine was not an irritant or corrosive for the skin and eye.
- On the basis of animal and clinical data, the FDA's CIR Expert Panel concluded that toluene-2,5-diamine was safe as a cosmetic ingredient in the present practices of use, which included colorants in permanent hair dyes and tints.
- They were unable to locate any reports where permanent damage resulted from use of phenylenediamines and toluenediamines in hair dyes.
- XXXXXXXX was the leading wholesaler of eyelash/eyebrow tinting products to retail shops in Australia since 1977 and had never received a safety related complaint. XXXXXXXX asserted that this reflected the clear instructions for use and safety

directions included with the product. XXXXXXXX endorsed the view that "the matter might be dealt with more appropriately by ensuring appropriate labelling".

- A selection of letters and emails from over 50 individuals highlighted concerns about the prohibitive costs of tinting eyebrows and eyelashes in salons. XXXXXXXX also asserted that there had also been an extensive number of phone calls from concerned individuals.

The Committee noted that a submission was also received from XXXXXXXX expressing concern about the continuing absence of eyebrow and eyelash tinting products. The Committee noted that XXXXXXXX supported the implementation of a new label warning for products containing phenylenediamine and toluenediamine, suggesting:

WARNING – This product contains phenylenediamine and toluenediame, which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

Members also noted that a submission had been received from XXXXXXXX seeking the views of the Committee on the safety directions (better described as "use instructions") for its product XXXXXXXX, an imported eyebrow and eyelash tinting product using silver nitrate. The Committee noted that XXXXXXXX had marketed XXXXXXXX for a number of years in Australia and New Zealand and that sale had been stopped in Australia since the prohibition on sale of these types of products containing phenylenediamine or toluenediamines, although XXXXXXXX does not contain these substances.

The Committee was advised that the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) was asked about the appropriateness of the safety instructions for XXXXXXXX and whether it represented a safer alternative to similar products containing phenylenediamines and toluenediamines. The Committee noted that the NICNAS evaluation highlighted the following:

- Of the ingredients in XXXXXXXX two did not appear on the Australian Inventory of Chemical Substances (AICS). This meant that the products containing these chemicals are not allowed to be sold in Australia before they are notified to NICNAS. The issue of AICS listing was to be discussed directly with the importer by NICNAS.
- Two ingredients were scheduled: ammonium hydroxide and silver nitrate. NICNAS concluded that it was likely that XXXXXXXX should be labelled as a Schedule 6 (Poison) based on the silver nitrate content. There was no such labelling on the package sample.
- The toxicological data in the NICNAS report on the XXXXXXXX ingredients showed that three of the ingredients are severe eye or skin irritants, although the concentrations of these chemicals in the product were unknown. The Evaluator noted

that advice on the safety of the product in comparison to phenylenediamines and toluenediamines could not be made because of lack of formulation and toxicity data.

- NICNAS also noted a number of issues with the product instructions relating to inconsistencies, clarity and missing information.

The Committee also noted a submission from XXXXXXXX in favour of the use of its eyelash and eyebrow tinting products in Australia. XXXXXXXX supported new labelling directions for allowing use in the home, as well as for salon and professional use. The Committee was advised that since 2000 XXXXXXXX had sold in excess of 5 million units of its product and during that time that there have been only 65 complaints about these products including eye irritation and allergic reactions. The members also noted that included in the submission was a letter from XXXXXXXX indicating no reported incidents of injury during use.

The Committee noted a submission from XXXXXXXX in support of the foreshadowed option allowing home and salon use. XXXXXXXX highlighted the time and economic impact of going to salons versus home use of these products.

The Committee noted a further public submission was received from XXXXXXXX which detailed XXXXXXXX experience with dying at salons and provided a yearly estimate for this procedure of $839.50. XXXXXXXX also asked the Committee to again consider XXXXXXXX submission to the February 2005 NDPSC meeting. This submission outlined concerns about the withdrawal of a product and XXXXXXXX's preference for home use over salon use. XXXXXXXX considered that appropriate warnings would be a more suitable response to any danger presented by this product, and that removing the product from the market was likely to have negative side-effects as people sought alternatives.

The Committee also noted that submissions considered at previous NDPSC meetings asserted the following:

- Animal testing indicated that these dyes in short contact with eyes appeared to leave no permanent damage. The FDA's CIR Panel determined that m-phenylenediamine can be used at levels up to 5% after reviewing eye and skin irritaton and skin sensitization as well as other data from animal and human studies. 2-Chloro-p-phenylenediamine was considered not to be a skin irritant or skin sensitizer when assayed on abraded on intact skin.
- Toluenediamine was demonstrated to be a slight dermal irritant on rabbits at 2.5% but not with guinea pigs at 10%, however it was determined to be a sensitizer.
- Some members of the public made representations that they have been using the product for years and prefer home use over salon use because of convenience and expense.
- If eyelash and eyebrow tints are removed from sale, people are likely to purchase off-the-shelf hair dyes for the purpose, as they have similar but stronger ingredients.

Other undesirable results could include black market importing, under-the-counter trading, or the marketing of home-made products.

- In the professional situation, the patients are screened for allergenicity to the products through patch testing. Recent problems have come about because Professional Use Only products were being sold directly to the public.
- In the USA, Canada and the European Union there are requirements for cautionary statements but not an actual ban on phenylenediamines and toluenediamines. Some state legislature of the USA regulate licensing and training of professionals in the safe use of products for eyelash and eyebrow tints, in the same manner as the Commonwealth training modules in this area.

Two members advised the Committee that they had reviewed the training material for salon use of eyebrow and eyelash tinting products. The members noted that the national training modules in this area were an outcome of a programme where a committee was charged with the development of nationally consistent training material for salons. The XXXXXXXX and XXXXXXXX representatives undertook to approach, on behalf of the NDPSC, this national committee to request to have the material reviewed and amended given that there were inconsistencies including statements to the effect of "assure people that absolutely no harm will result from the use of the product" being followed by contradictory assertions like "please tell me if this product is stinging or burning your eyes".

A member expressed some reservations about self application in the home setting and suggested that perhaps manufacturers should be encouraged, in developing the home use instructions, to indicate that the product should not be self applied and that the user should seek another person's assistance in applying the product.

A member noted that the proposed warning statement included "…a preliminary test according to the accompanying directions…". While the Committee generally agreed that this wording compels products to have directions for use a member enquired as to how the Committee could be satisfied as to quality of these accompanying directions given that there would be no mandated rules in the SUSDP about what the accompanying directions need to contain. The Committee was advised that the "accompanying directions" requirement was modelled on what currently applies to hair dyes containing phenylenediamines and toluenediamines and that no particular issues have arisen relating to the quality of these use directions and industry appears to be reliably self regulating on this issue at the moment.

The Committee generally agreed that while there was no national regulator for these products, the quality of the "accompanying directions" would be a jurisdictional matter, subject to Common Law and subject to fair trading and consumer affairs regulations. Additionally, if the directions prove to be inadequate the Committee could reconsider the scheduling of phenylenediamines and toluenediamines in the future.

A member also enquired about whether there was a need to consider concentration cut-offs in the schedule entry or could the Committee presume that the companies would market appropriate concentrations. The Members noted that eyebrow and eyelash tinting products contained significantly lower concentrations of phenylenediamines and toluenediamines than the hair dye products and agreed that concentration wasn't currently an issue, particularly as the main safety concern was allergenicity.

The Committee agreed that while phenylenediamines and toluenediamines were only moderately irritant to the skin and are not corrosive to the eye, they were clearly sensitisers with the potential to cause a strong allergic response, although there was no evidence to suggest that serious adverse effects were common. The Committee was aware of only a few cases and one member asserted that while there has been huge marketing of phenylenediamines and toluenediamines for a large number of years, noting that one submission indicated that 5 million applications had been sold internationally, there have been remarkably low levels of adverse reaction reports. The Committee thus considered that eyelash and eyebrow tinting products could be made available for home and salon use provided they carry strong label warnings and clear safety directions.

The Committee agreed that the labelling in the foreshadowed amendments which allowed the use of eyebrow and eyelash tinting products in salons and the home would be of sufficient strength to reduce the potential harm consistent with Schedule 6 requirements. However, the Committee had some residual concerns about eyebrow and eyelash tinting products containing phenylenediamines and toluenediamines and agreed that this will need to be watched in the future.

DECISION 2005/44 - 8

The Committee noted that while phenylenediamines and toluenediamines were only moderately irritant to the skin and are not corrosive to the eye, they were clearly sensitisers and that the potential risk of causing a strong allergic response in a small number of individuals could be minimised through appropriate labelling. The Committee therefore agreed to:

- amend the entries for phenylenediamines and toluenediamines in Schedule 6 to allow the use of eyebrow and eyelash tinting products in salons and the home when appropriately labelled; and
- include in Appendix C other preparations containing phenylenediamines and toluenediamines for eyebrow and eyelash tinting which would not be covered by the Schedule 6 entry.

Schedule 6 - Amendment

PHENYLENEDIAMINES – Amend entry to read:

† PHENYLENEDIAMINES and alkylated phenylenediamines not elsewhere specified in these Schedules:

(a) in preparations packed and labelled for photographic purposes;

(b) in preparations packed and labelled for testing water **except** tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

(c) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

(d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING - This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

TOLUENEDIAMINE – Amend entry to read:

TOLUENEDIAMINE:

(a) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

(b) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING - This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix C –Amendment

PHENYLENEDIAMINES – Amend to read:

PHENYLENEDIAMINES in preparations for skin colouration and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

Appendix C – New entry

TOLUENEDIAMINE in preparations for skin colouration and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

4.4 PINE OILS

PURPOSE

The Committee considered:

- the inclusion of a general entry for pine oils when packed and labelled as a herbicide in Schedule 6 with a concentration cut-off to Schedule 5; and
- the deletion of Juniper berry oil, fir needle oil (Canadian), fir needle oil (Siberian) and *Pinus sylvestris* (Pine needle) oil from Appendix B.

BACKGROUND

Pine oils had been removed from Appendix B at the May 1995 NDPSC meeting due to a lack of data indicating safety in human use being received by the Committee during a review of essential oils.

The scheduling of pine oils with regard to use as a herbicide was considered at the February 2004 NDPSC meeting. XXXXXXXX applied for an extension of use for their home garden product, XXXXXXXX (containing XXX g/L pine oil derived from *Pinus radiata*), to allow commercial broad acre use. Once applied to target plants, this product removes the waxes from the outer skin of the foliage which promotes dehydration and plant death.

The February 2004 NDPSC meeting noted that an OCS evaluation report identified the product XXXXXXXX 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 oil derived from *Pinus radiata* in Schedule 6 when packed and labelled for use as a herbicide. The entry for pine oils was included in SUSDP 19 Amendment No 1, effective 1 September 2004.

At the October 2004 meeting, XXXXXXXX submitted new studies on eye irritancy and dermal toxicity in rabbits for the concentrated product (XXX%) and two ready-to-use premixes (XXX% and XXX%). The sponsor sought reconsideration of the scheduling of pine oils with a view to the Committee setting a cut-off to Schedule 5. Based on the data provided in the OCS evaluation report, the Committee agreed to include pine oils derived from *Pinus radiata* at 20 per cent or less in Schedule 5 when packed and labelled for use as a herbicide. This revised entry was published in SUSDP Amendment No 3, effective 1 May 2005.

However, pine oils are a common fragrance ingredient in consumer products and 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. Accordingly, Members sought information on other uses of pine oils from APVMA, XXXXXXXX, and XXXXXXXX.

At the February 2005 meeting Members noted advice provided by XXXXXXXX which indicated that use of pine oils in the cosmetic and fragrance industry was largely confined to that of a freshness component in fragrances at relatively low levels, well below 5%. Product sizes could range up to 350 mL, but with very low levels of pine oils. The Committee also noted the information provided by XXXXXXXX which indicated that the content of pine oils in pest control, personal care, cleaners and disinfectant products does not generally exceed 10%. The Committee also acknowledged the information provided for consideration by the APVMA regarding pine oils in agricultural products and that there were some registered products just above the 20% pine oil concentration.

Members noted that the APVMA was unable to determine whether the pine oils in agricultural products were derived from *Pinus radiata*. A number of products registered as containing pine oil had reference to CAS No. 8002-09-3 which refers to Dwarf pine oil/Yarmor pine oil. The Committee noted that it was difficult to definitively identify the source as bulk-purchase pine oils was generally supplied from a variety of sources, which may or may not include *Pinus radiata*. On this basis, the Committee considered that it was not appropriate to specify the source species; if other pine oils were not irritating to the eye, further scheduling applications would be considered.

The Committee agreed to foreshadow an amendment of the Schedule 5 and Schedule 6 pine oil entries to remove reference to *Pinus radiata*, and to foreshadow the removal of juniper berry oil, fir needle oil (Canadian), fir needle oil (Siberian) and *Pinus sylvestris* (pine needle) oil from Appendix B. The decision to schedule pine oil herbicides as a class was taken due to the skin and eye irritancy of pine oils; and on the grounds that the source of the pine oils often cannot be determined. The decision to remove the other oils from Appendix B was taken on the grounds that the Committee had insufficient information to determine their complete safety profile but experience did not warrant scheduling at this time.

DISCUSSION

The Committee noted the following points considered at the February 2005 NDPSC meeting:

- The list of products containing pine oils provided by APVMA showed a number of products that would be captured by the foreshadowed Schedule 6 amendment. It was noted that there were also products at just above 20% pine oil concentration and it was argued by XXXXXXXX that there was unlikely to be a substantive difference in eye irritancy between these products and products containing 20% pine oils. On this basis a 25% cut-off to the Schedule 5 entry was suggested as being appropriate. The Committee generally agreed that a higher cut-off of 25 % was acceptable for herbicide products.
- The Committee considered that other pine oil products were unlikely to be hazardous on the basis of their use-pattern. Therefore it was considered that at present, only herbicidal products needed to be scheduled.
- The Committee noted that the terms of reference for the essential oils working party related to acute LD_{50} data in the rat, and oils were scheduled on this information in the context of the use in aromatherapy. The Committee observed that the present use, on a large scale as a herbicide, was not considered by the working party.
- Members noted that the related substances fir needle oil (Canadian), fir needle oil (Siberian), and *Pinus sylvestris* (pine needle) oil were currently in Appendix B, and that each of these oils has an acute oral LD_{50} value of >5g/kg body weight. These oils had been exempted from the requirements of scheduling on the basis of their low oral

toxicity, as determined by the Essential Oils Working Party, but other data such as eye irritancy had not been considered.

The members also noted that a submission had been received from XXXXXXXX which, while having no specific comment, registered an interest in the foreshadowed proposal.

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The Committee agreed to schedule pine oil herbicides as a class in Schedule 6 due to the skin and eye irritancy of pine oils and on the grounds that the source of the pine oils often cannot be determined. The Committee further agreed to a cut-off for preparations containing 25% or less of pine oil herbicides to Schedule 5 on the grounds that at this concentration the substance was expected to have a low toxicity profile.

The Committee also agreed to delete the Appendix B entries for fir needle oil (Canadian), fir needle oil (Siberian), and *Pinus sylvestris* (pine needle) oil. This decision was taken on the grounds that the Committee had insufficient information to determine their complete safety profile but experience did not warrant scheduling at this time unless used as herbicides.

Schedule 5 - Amendment

PINE OILS – amend entry to read:

PINE OILS in preparations containing 25 per cent or less of pine oils when packed and labelled as a herbicide.

Schedule 6 - Amendment

PINE OILS – amend entry to read:

PINE OILS when packed and labelled as a herbicide **except** when included in Schedule 5.

Appendix B – Amendment

JUNIPER BERRY OIL – delete entry

FIR NEEDLE OIL (Canadian) – delete entry

FIR NEEDLE OIL (Siberian) – delete entry

PINUS SYLVESTRIS (PINE NEEDLE) OIL – delete entry

4.5 GLYCOLIC ACID

PURPOSE

The Committee considered the scheduling of glycolic acid.

BACKGROUND

Glycolic acid is an alpha-hydroxy organic acid that has been used cosmetically in topical preparations for the treatment of hyperpigmentation and photodamaged skin. Glycolic acid also has a use in agricultural products as a disinfectant and pesticide.

Glycolic acid in cosmetic products was considered at the November 1999, May 2000 and August 2000 NDPSC meetings following assessment under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Priority Existing Chemicals Program. At the August 2000 Meeting an entry for glycolic acid was included in Schedule 6 with an exemption for preparations containing 20 per cent or less of glycolic acid and a pH of 3.5 or greater. Glycolic acid was scheduled on the basis of its corrosive irritation potential when applied to the skin or inadvertent contact with the eyes.

At the February 2005 NDPSC meeting the Committee considered a recent review of the First Aid Instructions and Safety Directions (FAISD) Handbook by the OCS which identified an inconsistency in the scheduling of glycolic acid. The OCS review identified several agricultural products which would be unscheduled as the Schedule 6 entry for glycolic acid only covered cosmetic use. The OCS recommended that the entry be modified to include products used in agriculture such as pesticides. Additionally, it was proposed that the existing scheduling exemptions could be applied to agricultural products.

The Committee agreed to an amendment to the Schedule 6 entry for glycolic acid to include its use in agricultural chemicals on the basis of glycolic acid's corrosive irritation potential to the skin and eyes. The Committee also agreed that the current exemptions remain appropriate given the use pattern in agricultural products.

A view was expressed that producers and users of some of the products affected by the proposed scheduling amendment may not have made submissions to the February 2005 Meeting because they did not consider routinely these products to be agricultural chemicals. The Committee agreed that, while the products would be clearly defined as agricultural chemicals under *The Agricultural and Veterinary Chemicals Code Act 1994*, it was appropriate to allow further opportunity for industry comment by foreshadowing consideration of the scheduling of glycolic acid at the June 2005 meeting.

DISCUSSION

The Committee noted the following information from the February 2005 NDPSC meeting. The OCS FAISD Handbook review found 13 registered products containing

glycolic acid. The Members were advised that a recent search of PUBCRIS indicated that there were currently 12 products containing glycolic acid registered with the AVPMA. These products were mainly detergents and sanitisers for the dairy industry. Of these products, there would probably be regulatory impact for 3 products which were currently labelled Schedule 5. There would also be regulatory impact on a buffer and wetting agent currently labelled as unscheduled. There would be no regulatory impact for the 6 products which are already Schedule 6 on the basis of other constituents. There was also likely to be no regulatory impact on the remaining 2 products which had glycolic acid concentrations below the proposed cut-off.

The Committee also noted a submission from A XXXXXXXX which advised that three member companies market dairy cleaner/sanitiser products registered by the APVMA that contain glycolic acid. XXXXXXXX had received no objections from its member companies on the foreshadowed decision.

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The Committee agreed to the foreshadowed amendment to the Schedule 6 entry for glycolic acid to include its use in agricultural chemicals on the basis of glycolic acid's corrosive irritation potential to the skin and eyes. The Committee also agreed that the current exemptions remain appropriate for agricultural products apart from (a) which only applies to cosmetic preparations.

Schedule 6 - Amendment

GLYCOLIC ACID – amend entry to read:

GLYCOLIC ACID (including its salts and esters) in cosmetic products or when packed and labelled for use as an agricultural chemical **except**:

(a) in cosmetic preparations for salon use only which are labelled in accordance with the National Occupational Health and Safety Commission's *National Code of Practice for the Labelling of Workplace Substances* [NOHSC:2012 (1994)] or its successors;

(b) in preparations containing 5 per cent or less of glycolic acid; or

(c) in preparations containing 20 per cent or less of glycolic acid with a pH of 3.5 or greater.

4.6 CARBAMIDE PEROXIDE / HYDROGEN PEROXIDE

PURPOSE

The Committee considered the scheduling of carbamide peroxide and hydrogen peroxide.

BACKGROUND

CARBAMIDE PEROXIDE

Carbamide peroxide is a one-to-one ratio of urea and hydrogen peroxide. 10% carbamide peroxide is equivalent to 3.62% hydrogen peroxide. Carbamide peroxide releases oxygen on contact with moist tissues and is used to treat infections of the ear, mouth, skin, and mucous membranes and for softening and removal of ear wax.

At the February 2005 NDPSC meeting the Committee considered concerns referred by XXXXXXXX that some tooth whitening products, being distributed or sold on the internet, contained up to 35% carbamide peroxide. XXXXXXXX considered the use of over 15% carbamide peroxide products by non-professionals as dangerous.

Members were of the view that, despite carbamide peroxide being a source of hydrogen peroxide, industry may not appreciate the scheduling requirements for this substance and consequently not appropriately label these tooth whitening products. A member advised that the carbamide peroxide tooth whitening products currently on the market, whether produced in Australia or imported, were not likely to be compliant with the current Schedule 5 and Schedule 6 labelling for hydrogen peroxide. On that basis, the Committee agreed that specific entries in the SUSDP for carbamide peroxide would be appropriate. A member also drew the Committee's attention to a European Commission report which limits toothpaste and mouthwash products to 0.1% hydrogen peroxide. The Committee agreed that oral hygiene products of this strength were of little risk and did not warrant scheduling.

The Committee agreed to foreshadow the inclusion of carbamide peroxide in Schedules 5 and 6 and Appendices E and F of the SUSDP to align it with the current hydrogen peroxide scheduling. Furthermore the Committee agreed to foreshadow an amendment to the hydrogen peroxide entries in Schedule 5 and 6 to include a cut-off for oral hygiene products such as toothpaste and mouthwash. Members also agreed that the current carbamide peroxide products for removing ear wax would not require a Schedule 2 entry as the use pattern of these products involved little risk while noting that any substantially higher strength formulations would be covered by the proposed Schedule 5 and 6 entries.

HYDROGEN PEROXIDE

At the August and November 1993 NDPSC meetings the Committee considered a review of the toxicity of hydrogen peroxide and agreed that hydrogen peroxide be exempt from scheduling at 3% or less, classified as Schedule 5 from 3% up to 6% and all other

concentrations placed in Schedule 6. The Committee particularly noted the following toxicology data in reaching this decision:

- Hydrogen peroxide has moderate acute toxicity at high concentrations. Rat studies set oral LD_{50}s for 10% hydrogen peroxide at 1500 mg/kg, 35 % at 1200 mg/kg and 60% at 800 mg/kg. Rabbit studies gave dermal LD_{50}s for 35% hydrogen peroxide at 2000 mg/kg and 90% at 690 mg/kg. Rat studies gave a dermal LD_{50} for 90% hydrogen peroxide as 4060 mg/kg. Inhalation toxicity of hydrogen peroxide in rats was considered low at low concentrations.
- Rabbit studies found no skin irritation for 3-8% hydrogen peroxide, slight irritation for 10-35% and corrosive irritation for 50-70%. Rabbit studies also found slight eye irritation for 5% hydrogen peroxide, moderate (unwashed eye) to severe (washed eye) for 8%, severe for 10% and corrosive irritation for 35-70%. Guinea pig tests using 16% hydrogen peroxide showed no skin sensitisation.
- In humans it had been reported that ocular and respiratory effects could be serious at concentrations of greater than 10 %, 35 % and 40 % preparations in domestic accidents had been associated with mortality in children, and permanent injury had occurred in an adult with 35 %.

At the April and November 1994 and May 1995 NDPSC meetings the Committee agreed to amend the scheduling of hydrogen peroxide through inclusion of exemptions for hair preparations: 6% or less for the Schedule 5 entry because of the packaging and low exposure potential; and 12% or less for Schedule 6 allowing capture of hair dye preparations containing > 6% up to 12% of hydrogen peroxide in Schedule 5. The Committee also agreed that the hydrogen peroxide concentration would determine the appropriate warning statements.

At the February 2002 NDPSC meeting the Committee considered the need for First Aid Instructions on hair dye products containing hydrogen peroxide and agreed that the existing labelling requirements specified in the SUSDP for products containing hydrogen peroxide remained appropriate on public health and safety grounds.

DISCUSSION

The Committee was advised that at the February 2005 NDPSC meeting it had requested a copy of the European Union Cosmetics Standard – The International Nomenclature of Cosmetic Ingredients (INCI). The Secretariat advised that this resource was online at http://pharmacos.eudra.org/F3/inci/index.htm.

The Committee recalled that at the February 2005 NDPSC meeting it considered the following:

- The European Commission's Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) had recommended that the content of hydrogen peroxide in tooth whitening products should not exceed 6 % (present or

released) with a 50 mg a day limit. Use of tooth whitening products was not recommended prior to or immediately after dental restoration and that conditions such as pre-existing tissue injury or concurrent use of tobacco and/or alcohol may exacerbate the toxic effects of hydrogen peroxide. The SCCNFP concluded that the proper use of tooth bleaching agents containing 0.1 to 6.0 % hydrogen peroxide (or equivalent for hydrogen peroxide releasing substances) was safe if used under the supervision of a dentist.

- Various reports which indicated that tooth, soft-tissue and/or gingival sensitivity was very common when using peroxide generating tooth whitening products including carbamide peroxide. Other common side effects were enamel damage and increased marginal leakage of an existing restoration. Adverse reactions also included the possible overgrowth of opportunistic organisms with prolonged use. A report indicated that the hydroxyl radical by-product of carbamide peroxide had been associated with periodontal tissue damage and root resorption.

Public Submissions were received from XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX.

The XXXXXXXX submission recommended that the Committee:

- delete from the foreshadowed Schedule 5 and 6 entries the cut-off "dental hygiene products for the whitening of teeth, containing 0.3 [0.1] per cent or less of carbamide peroxide [hydrogen peroxide]";
- amend the "in other preparations" in the foreshadowed Schedule 5 and 6 entries from 9 to 10% or less of carbamide peroxide; and
- review the first aid statements to ensure that they were appropriate for the oral hygiene use.

These issues are discussed under "Lower Cut-Off", "Ratio" and "Standard Statements" below.

The XXXXXXXX submission requested a reconsideration of the Schedule 5 and 6 entries for carbamide peroxide so as to exclude products containing 10% carbamide peroxide from scheduling [see discussion under "Ratio" below]. The Members noted that amongst the data submitted by XXXXXXXX was:

- A claim that there was no data suggesting that products containing 10 % carbamide peroxide are not safe to use as currently marketed (that is, without a cautionary signal heading as a warning).
- Literature references and mention of unpublished randomised controlled trials conducted by XXXXXXXX that were claimed to support the efficacy and safety of carbamide peroxide.
- Information to the effect that the most common side effect, dental hypersensitivity, was transient in nature with no persistent pain or irritation after discontinuation of treatment.

- Information to the effect that while some studies had demonstrated a reduced enamel bond strength post bleaching, it was generally recommended (on label and consumer information leaflet) that any bonding restorative procedures be delayed for up to 1 week post dental bleaching.
- Mention of studies that have demonstrated that the level of salivary hydrogen peroxide declines quite rapidly following use of peroxide containing dental whiteners.
- Information that the safety of carbamide peroxide was supported by a long history of use in professionally applied dental bleaching products at concentrations up to 35%.
- Information that the requirement to include "CAUTION" as a signal heading on products containing 10% carbamide peroxide would only induce fear in consumers.

The XXXXXXXX submission proposed the retention of the existing schedule entries for hydrogen peroxide with a consistent new entry for carbamide peroxide (i.e. deletion of the "dental hygiene products for the whitening of teeth, containing 0.3 per cent or less of carbamide peroxide" from the foreshadowed decision [discussed under "Lower Cut-Off" below] and leaving the hydrogen peroxide entry as it currently exists in the SUSDP].

The members noted XXXXXXXX's assertion that the scheduling of carbamide peroxide could not be considered without first considering the safety of hydrogen peroxide. The Committee noted that XXXXXXXX had provided data on the safety and regulation of hydrogen peroxide, including:

- Various studies including a clinical efficacy study that supported the safety of hydrogen peroxide.
- The observation that since the EU's introduction of the 0.1% limit for hydrogen peroxide, the SCCNFP had not only stated that products containing > 0.1 - 6% hydrogen peroxide were considered safe after consultation with a dentist, but the EU was working on a proposal that tooth whitening products containing up to 6% hydrogen peroxide could be marketed over the counter, and that safety would be addressed via a labelling statement.
- As documented in the May 2003 US Federal Register, the FDA Non Prescription Drugs Advisory Committee conducted a review of the overall safety of hydrogen peroxide in oral care products, and considered that hydrogen peroxide was safe at concentrations up to 3% for everyday use.
- Advice sought from XXXXXXXX concerning the safety of hydrogen peroxide in dentifrices and mouthwash products. XXXXXXXX's reports supported the safety of home oral health care products which contain low concentrations of hydrogen peroxide (up to 3%) and that low concentrations of hydrogen peroxide neither damages oral hard or soft tissues, nor do they pose a significant risk of adverse long term effects.
- XXXXXXXX noted, however, that in high concentrations hydrogen peroxide may have transient effects on the tooth itself and may also affect some dental materials.

Soft tissues exposed to high concentrations of hydrogen peroxide for short periods may show chemical injury in the form of erythema or mucosal sloughing, while exposure for prolonged periods may cause inflammation or hyperplasia.

- With regard to mouth rinses, XXXXXXXX noted that from the literature it could be concluded that hydrogen peroxide mouth rinses (at concentrations up to 3%) did not damage teeth or oral mucosal tissues. The Committee noted details of several commercially available mouth rinses containing hydrogen peroxide.
- That XXXXXXXX had a number of products currently supplied in the Australian market that would be impacted upon by the foreshadowed scheduling changes.
- XXXXXXXX's assertion that the exposure to hydrogen peroxide from the use of XXXXXXXX, which delivers 1% hydrogen peroxide, was in the order of 2.5 mg compared to the 50 mg limit recommended by the SCCNFP.

Members also considered a proposal that XXXXXXXX submitted to amend the standard statements for hydrogen peroxide in Appendix E (see discussion under "Standard Statements" below).

The Committee noted a submission from XXXXXXXX registering an interest in the foreshadowed proposal.

The Committee discussed the information provided in the context of the following 3 specific issues:

Lower Cut-Off

The Committee considered the cut-off in the foreshadowed Schedule 5 and 6 entries for "dental hygiene products for the whitening of teeth, containing 0.3 [0.1] per cent or less of carbamide peroxide [hydrogen peroxide]".

The Committee noted that the lower limits for dental hygiene products for the whitening of teeth were included in the foreshadowed decision so as to avoid the inadvertent capture of toothpastes and mouthwashes. This limit was based in part on the SCCNFP report's limit for general oral hygiene product which was 0.1% hydrogen peroxide. The Committee agreed that oral hygiene products of this strength were of little risk and did not warrant scheduling.

The Committee noted, however, that the FDA Non Prescription Drugs Advisory Committee review and XXXXXXXX's reports supported use up to 3% hydrogen peroxide as safe. The Committee agreed to remove the lower cut-offs in the foreshadowed Schedule 5 and 6 entries on the grounds that the data considered at the meeting indicates that in oral hygiene products at concentrations less than or equal to 3% hydrogen peroxide hydrogen peroxide was safe for the intended use pattern.

Ratio

The Committee considered whether to confirm the use of the foreshadowed carbamide peroxide values, which were based on a 3:1 ratio conversion from the hydrogen peroxide values, or to have the carbamide peroxide values reflect the exact 2.76:1 ratio conversion from hydrogen peroxide.

A member argued that, while in general rounding was accepted practice for scheduling, this was one of those rare occasions where one scheduling entry was making reference to another and as such the two entries should be equivalent. The Committee noted, however, that this view was not based on any expected toxicological difference when using either ratio conversion, but was solely to match the hydrogen peroxide entry.

The Committee generally agreed that the use of a simple 3:1 ratio would provide clarity to industry, promote compliance and would not introduce any significant toxicological risk through the marginal rounding up. The Committee thus agreed to confirm the use of a 3:1 ratio for converting the hydrogen peroxide values to carbamide peroxide on the basis of simplicity and clarity.

The Committee also considered the XXXXXXXX and XXXXXXXX requests that, rather than rounding to the foreshadowed 9% when converting the 3% hydrogen peroxide to a carbamide peroxide equivalent, the Committee round to 10% on the basis that this would have less of a regulatory impact on industry. The Committee noted that, based on the exact ratio for hydrogen peroxide content in carbamide peroxide, the exemption cut-off should be 8.3%.

The Committee agreed that rounding up to a 9% limit was acceptable – noting that the difference between 8.3% and 10% was not insignificant and hence the proposed carbamide peroxide and existing hydrogen peroxide Schedule 5 cut-offs remained appropriate. The Committee agreed that any argument for increasing a cut-off for the Schedule 5 carbamide peroxide entry would need to be based either on data for carbamide peroxide or an argument using hydrogen peroxide. Any change to the carbamide peroxide entry would also need to be reflected in the hydrogen peroxide entry which drives the scheduling and labelling of these products.

Standard Statements

The Committee noted that the foreshadowed Appendix E standard statements and the Appendix F safety directions and warning statements for carbamide peroxide were directly analogous to hydrogen peroxide. The Committee, however, considered proposals by XXXXXXXX and XXXXXXXX that for oral hygiene products that contain carbamide peroxide the standard statements S1 and E2 in Appendix E should be reviewed. The Committee noted XXXXXXXX's assertion that when S1 was used on labelling for tooth whitening products the statement "if skin contact occurs…" was not a meaningful communication to the consumer. Given that the product would have contact with the skin on the inside of the cheek, XXXXXXXX suggested that for products that

contain hydrogen peroxide, which are used in the mouth, S1 and E2 could be replaced by an appropriate revised statement.

The Members were advised that S1 and E2 currently only apply to hydrogen peroxide concentrations more than 3% and that E2 does not refer to skin exposure. Members were further advised that the current S1 and E2 standard statements were:

S1 If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

E2 If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by the Poisons Information Centre or a doctor, or for at least 15 minutes.

The specific concern the Members considered was whether S1 was relevant to Schedule 5 oral hygiene products containing hydrogen peroxide or carbamide peroxide. A member noted that none of the standard statements really appeared relevant to the mouth. A member suggested that a new S1 could apply, to those products with 9 to less than or equal to 18% carbamide peroxide for oral use, to the effect of "rinse mouth with water after use", rather than the current A, G3, E2 and S1 standard statements mandated for the analogous hydrogen peroxide products.

A member noted, in support of the need for a mouth specific standard statement, that data from XXXXXXXX's report indicated that there were isolated reports of patients who have developed oral ulcerations after using 3% hydrogen peroxide for 1-2 minutes, 3-5 times daily, while at lower concentrations, changes are less marked or inconspicuous even with continuous exposure. The Committee, however, in considering the applicability of a new standard statement, noted that the varied formulation of these products – with some products require use for an extended period while others were compatible with immediate rinsing – posed difficulties for developing a mouth specific standard statement.

A member also noted that it made no practical difference to "rinse the mouth out with water" because in normal use with oral hygiene products equivalent to between 3 and 6 % hydrogen peroxide exposure in the oral cavity is generally limited since hydrogen peroxide undergoes rapid decomposition i.e. after 1 minute of brushing less than 20 % of hydrogen peroxide introduced into the oral cavity can be recovered according to one submission. A member further noted that most people were going to rinse their mouth out when finished even without a direction to do so.

The Committee generally agreed that reliance could be placed on the packaging, relevant to the product, to give the directions in relation to how long the consumer uses it and whether rinsing was required and that for appropriate use there appeared little need for standard statements S1 and E2 up to the equivalent of 6% hydrogen peroxide for oral hygiene use.

The Committee noted, however, that the above arguments all considered the standard statements in the context of were they relevant for use in the mouth. The Members agreed that in considering standard statements the Committee needed to not only consider the direct toxicity in normal use, but also situations of inappropriate use. A member illustrated this with a scenario where a child, through playing with a tooth whitening product, received a dermal or eye exposure and that the standard statements would direct a parent to appropriate action. The Committee observed that the skin and eye irritation data for hydrogen peroxide, as set out in the background, supported a moderate risk from Schedule 5 hydrogen peroxide products.

The Committee confirmed that the existing labelling requirements specified in the SUSDP for products containing hydrogen peroxide remained appropriate on public health and safety grounds and on the basis of the toxicology data. The Committee also confirmed that the labelling requirements for carbamide peroxide should reflect those of the analogous hydrogen peroxide entries. The Committee further confirmed that the standard statements of carbamide peroxide and hydrogen peroxide in formulations for oral hygiene are to reflect the current standard statements for hydrogen peroxide as, despite the intended use these statements are also intended to aid people who need direction in dealing with circumstances such as skin or eye exposure through inappropriate use.

The Committee, taking into account the public submissions, confirmed that the current scheduling of hydrogen peroxide remained appropriate on the basis of the toxicity. The Members also concurred with the conclusion at the February 2005 NDPSC meeting that, despite carbamide peroxide being a source of hydrogen peroxide, industry had not always recognised the scheduling ramifications of this and as a consequence there were some inappropriately labelled tooth whitening products. On the basis of the hydrogen peroxide toxicity profile and the need for clarity, the Committee agreed to confirm the inclusion of specific entries for carbamide peroxide in the SUSDP.

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The Committee agreed to the inclusion of carbamide peroxide in Schedules 5 and 6 and Appendices E and F of the SUSDP to align it with the current hydrogen peroxide scheduling. The Committee also agreed to use a ratio of 3:1 for the conversion from hydrogen peroxide values to carbamide peroxide values on the basis of simplicity and clarity. The Committee further agreed to confirm the existing schedule entries for hydrogen peroxide on the basis of its toxicological profile.

Schedule 5 – New entry

CARBAMIDE PEROXIDE in preparations containing 18 per cent or less of carbamide peroxide **except** in preparations containing 9 per cent or less of carbamide peroxide.

Schedule 6 – New entry

CARBAMIDE PEROXIDE **except**:

(a) when included in Schedule 5; or

(b) in other preparations containing 9 per cent or less of carbamide peroxide.

Appendix E, Part 2 – New entry

Poison	Standard Statements
Carbamide peroxide	
• more than 9 per cent up to 60 per cent	A,G3,E2,S1
• more than 60 per cent	A,G1,G3,G4,E2,S1

Appendix F, Part 3 – New entry

Poison	Warning Statement	Safety Directions
Carbamide peroxide		
(a) more than 9 per cent up to 30 per cent	5	1
(b) more than 30 per cent up to 60 per cent	5	2
(c) more than 60 per cent	2	2,4

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

5.1 SUSDP, PART 4

5.1.1 POTASSIUM AZELOYL DIGLYCINATE

PURPOSE

The Committee considered the scheduling of potassium azeloyl diglycinate (PAD).

BACKGROUND

At the August 1995 NDPSC meeting a new entry for azelaic acid was made in Schedule 4 following registration approval of a topical preparation containing azelaic acid. Azelaic acid is used by dermatologists as an anti-seborrheic, anti-acne and anti-micotic.

At the November 1996 NDPSC meeting the Committee considered a request for rescheduling a cream preparation containing 20% azelaic acid, for the treatment of acne vulgaris, from Schedule 4 to Schedule 3. Among the points considered by the Committee was that adverse reactions with azelaic acid appear to be minimal, limited to local reactions that are no greater than those of other freely available topical acne preparations such as benzoyl peroxide. It was also noted that the 20% formulation was no more toxic than 5% benzoyl peroxide formulations which were included in Schedule 2. It was further noted that azelaic acid is produced naturally as an oxidation product of oleic acid and secreted by the sebaceous gland onto the skin, although the proposed cream was more concentrated that that normally present. The Committee agreed that inclusion in Schedule 2 for azelaic acid preparations for dermal use was appropriate in view of its toxicity and its use for an easily diagnosed condition.

At the February 1997 NDPSC meeting the Committee considered a comment received concerning the decision to reschedule azelaic acid for dermal use from Schedule 4 to Schedule 2. The comment raised concerns that Schedule 2 was not appropriate because of the need for diagnosis and counselling on regular use to obtain the best outcome with the product. The Committee was advised that inappropriate use and lack of counselling may result in severe skin reaction. The Committee noted the sponsor companies response, including that there would be adequate opportunity for on-going counselling when the patient returns to the pharmacy to purchase this medication, that support materials will be provided to the pharmacist and that the adverse effect profile of 20% azelaic acid cream compares favourably with 5% benzoyl peroxide which is included in Schedule 2. The Committee considered that this information adequately addressed the issues raised by the post-meeting comment and that Schedule 2 decision of the November 1996 meeting remained appropriate.

DISCUSSION

The Committee was advised that XXXXXXXX, on behalf of XXXXXXXX, submitted a request that PAD, a salt/derivative of azelaic acid, be exempt from the requirements of scheduling when used in cosmetic products at low concentrations.

The Committee noted that XXXXXXXX had a range of cosmetic products retailed in Europe and USA containing PAD and that it was seeking to retail these products in Australia. XXXXXXXX was currently unable to do this because PAD is a derivative of azelaic acid and was captured under Schedule 2 by the scheduling status of azelaic acid. The Committee noted that the proposed products are expected to use PAD at levels of between 0.25 and 1.0%.

The members were advised that there were four products on the ARTG containing azelaic acid as an anti-acne or anti-bacterial. These products had concentrations of azelaic acid from 15 to 20%. There were no products listed on ARTG using PAD.

The Committee noted advice from the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Some issues identified by NICNAS were:

- PAD was not listed on the Australian Inventory of Chemical Substances (AICS). NICNAS advised that the applicant was aware of this and that it was the applicant's intention not to notify the chemical to NICNAS until the NDPSC had made a decision on scheduling.
- The current data provided by the applicant was of a limited nature which did not enable a proper NICNAS assessment to support a recommendation on scheduling.

It was the view of XXXXXXXX that introducers of any new industrial chemical, including cosmetics, should first notify NICNAS for a decision regarding introduction of the chemical into Australia, before approaching other agencies. However, the Committee generally agreed that there was no basis to not consider an application put to it because the substance was not on AICS.

The Committee considered the toxicity data supplied by the applicant including a Het-cam test performed on the chorionallantoic membrane of hen's eggs which indicated that even at 100% concentration PAD was found to be a non-irritant to eyes. The members also considered that a test through occlusive application at a level of 7% active material to 20 humans found no skin irritancy or allergenic reaction.

The Committee generally agreed that the data as submitted was deficient in a number of areas, particularly noting:

- No oral toxicity studies; NICNAS estimated an oral $LD_{50} \geq 5000$ mg/kg, but this was an extrapolation from other substances.
- No dermal or inhalation acute studies.
- The eye irritancy test did not appear to be an OECD regulated test.
- The skin sensitization studies had limitations.
- No repeat dose, mutagenicity, carcinogenicity, reproductive toxicity or respiratory sensitisation studies.
- There were no photo sensitisation studies. No data on UV effect.

The Committee generally agreed that from the limited toxicity data PAD could be classified as exempt or Schedule 5 but the data did not provide the level of detail needed to support a definitive decision.

OUTCOME

The Committee, noting that the available toxicity data for PAD were deficient, agreed that the current scheduling of azelaic acid remains appropriate.

5.1.2 SODIUM POLYSTYRENE SULPHONATE

PURPOSE

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

BACKGROUND

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

SPS is the sodium salt of polystyrenesulphonic acid (PSS). The SPS polymer is highly charged with anionic sulphonic acid groups linked to aromatic rings of the polymer backbone.

SPS is used as a cationic exchange resin in human therapeutics (>99% SPS). SPS is currently the active used in a grandfathered listed medicine for treatment of hyperkalemia and hyperphosphatemia according to the ARTG. The function of the SPS in this therapeutic product was to treat high blood level potassium and high blood pressure potassium by removing potassium from the body by exchanging it with sodium in the gut. SPS is used as an excipient in four phentermine resin products.

SPS is also used as a raw material for cosmetics formulations overseas, including hair care (such as hair styling aid, thermal protective products, shampoos and conditioners) and anti-wrinkle skin care products. The therapeutic uses of SPS are substantially different from the cosmetic use. SPS is also used as emulsion stabilisers, film formers, surfactants and viscosity controlling agents.

DISCUSSION

The Committee was advised that while the AAN was polystyrene sulphonate – sodium the International Nomenclature of Cosmetic Ingredients name was sodium polystyrene sulphonate. The Committee was further advised that SPS was known under the following chemical names and CAS numbers:

- Benzenesulfonic acid, 4-ethenyl-, sodium salt, homopolymer CAS# 25704-18-1.
- Benzenesulfonic acid, ethenyl-, sodium salt, homopolymer CAS# 9080-79-9.

The Committee noted that a submission from XXXXXXXX, on behalf of XXXXXXXX, requested an amendment to the scheduling of SPS to exempt from Schedule 4 topical

cosmetic uses of this substance. The members noted that XXXXXXXX wished to import a product branded XXXXXXXX which contains SPS at a level of XXX%.

The Committee considered the XXXXXXXX submission's claims that there were a number of cosmetic benefits of SPS, particularly for hair products, including:

- Thermal protection of the hair up to 150 °C by the ingredient forming stable flexible films that are thermally stable.
- Static dissipation through the high charge density and aromaticity. Removal of cationic build-up on hair may also increase the perceived volume of hair.
- It is hydrophilic and easily rinsed off.

The Committee noted from the XXXXXXXX submission that cosmetic products using SPS were widely sold overseas. In particular, XXXXXXXX noted that XXXXXXXX was currently marketed in Europe and had been sold for over two years without any adverse reports. The members were advised that this product contained warning statements of – "Caution: Pressurised Container, Keep out of Reach of Children"; "Avoid Spraying near eyes"; and "Use only as directed".

The Committee considered XXXXXXXX's proposal for an amendment to the SPS Schedule 4 entry to read: "SODIUM POLYSTYRENE SULPHONATE for human therapeutic use".

The Committee noted the following points from the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) evaluation of the XXXXXXXX submission:

- The trade name of SPS was XXXXXXXX, an off-white powder consisting of 90% SPS.
- SPS was available in two forms: a water-soluble non-crosslinked form which appears to be used as the cosmetic ingredient (XXXXXXXX) and a cross-linked water-insoluble form in which was the form used in current therapeutic applications.
- Adverse reactions from therapeutic use came in two types – those associated with irritation and osmotic effects in the gastrointestinal tract (constipation, diarrhea, nausea etc.) and neuromuscular effects associated with potassium depletion (confusion, muscle weakness, irregular heatbeat).
- The high molecular weight of the polymer (XXXXXXXX, MW approximately 130,000) suggested poor absorption across biological membranes. The anionic charge suggests that the polymer might be expected to be a skin and eye irritant.

The members noted the evaluator's advice that limited toxicity information was submitted for SPS. The submitted data appeared to derive from MSDS sources and indicated that SPS has an acute oral toxicity LD_{50} in rat of >5 g/kg and a subchronic oral toxicity in rat of 90 day NOEL at an exposure of 1 g/kg. This information also included a

dermal LD_{50} >5 g/kg established from rabbit studies. However, no references were given.

The Committee considered the evaluator's note that the MSDS for XXXXXXXX from the supplier indicated the possibility of mechanical eye irritation from exposure to particles, mild irritation from repeated or prolonged skin contact and irritation of the gastrointestinal tract following ingestion. The members were advised that an exposure standard of 10 mg/m^3 on the basis of nuisance dust was noted.

The Committee also considered the evaluator advice that the information sheet for Flexan II noted suitability for spray applications with a droplet size greater than 50 micron and that safety evaluations of applications with particle sizes less than 50 micron have not been conducted. The information sheet claimed that full health and safety studies for the polymer are available on request. The Committee noted that these studies were not included in the submission.

The evaluator advised that the acute oral, intraperitoneal and subcutaneous toxicity of SPS appears low. Rat studies established a 4 hour LC_{50} 2.6 g/m3 with toxic effects of respiratory obstruction. These studies also established an oral LD_{50} > 8 g/kg, a subcutaneous LD_{50} > 15 g/kg and an intraperitoneal LD_{50} > 6 g/kg. Mouse studies established an oral LD_{50} > 10 g/kg, a subcutaneous LD_{50} > 15 g/kg and an intraperitoneal LD_{50} > 7 g/kg.

The members also noted that the evaluator had detailed additional safety studies of T-PSS, a high molecular weight, water soluble SPS. These studies reported that T-PSS (10%) was not considered a dermal sensitiser. Vaginal administration caused only mild irritation and no systemic toxicity. T-PSS was also determined to be non-mutagenic in vitro.

The Committee considered the following recommendations from the NICNAS evaluation report:

- Based on limited available data on different forms of SPS, given the low concentrations of SPS currently used in cosmetic products (< 10%) and the apparent low toxicity of SPS, the health risk associated with proposed topical cosmetic application of SPS (XXXXXXXX) in pump sprays or gels was likely to be low.
- However, a more reliable assessment of likely health effects from topical cosmetic use of SPS and a more informed recommendation regarding rescheduling would be possible on receipt of the full health and safety studies on XXXXXXXX which the supplier claims were available. In particular, it was noted that SPS is anionic and, therefore, a potential skin and eye irritant. This may be a cause for concern when using spray products.
- In the absence of the health and safety studies on SPS, an amendment to the scheduling for SPS cannot be supported.

The Committee noted the NICNAS recommendations. A member highlighted that, while the proposed uses are likely to pose a low hazard/risk and was probably either Schedule 5 or exempt, it was not possible using the submitted data to be definitive about a scheduling decision in terms of topical cosmetic use.

The Committee also noted that a public submission had been received from XXXXXXXX which advised that it uses SPS (bead form) in a sustained release formulation (phentermine capsules) where it is combined with the active drug to form a resin-drug complex, which imparts sustained release properties to the formulation. The submission requested the Committee consider the above in determining the scheduling of SPS.

OUTCOME

The Committee agreed, in the absence of health and safety studies on the product, that the current scheduling of sodium polystyrene sulphonate remains appropriate.

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

6.1 EMODEPSIDE AND PRAZIQUANTEL

PURPOSE

The Committee considered the scheduling of emodepside and praziquantel.

BACKGROUND

XXXXXXXX applied for approval of the new active ingredient emodepside, and registration of a product range called XXXXXXXX, containing XXX g/L emodepside and XXX g/L praziquantel (e.g. XXXXXXXX). This range is a topically applied liquid for XXXXXXXX and will be available in four different pack sizes (XXX, XXX, XXX mL single dose packs and a XXX mL multi-dose pack for use in veterinary clinics). All packs contain the same concentration of constituents. XXXXXXXX (ie all products in the range) is not registered in any overseas country at present, but it has been submitted to the EMEA (European Medicines Agency) for registration in the European Community where it is under review.

Emodepside is a pyrazino-isoquinoline derivative, a semi-synthetic derivative of PF1022A, a cyclic octadepsipeptide. PF1022A is a natural compound from the ubiquitous plant fungus *Mycelia sterilia*. Both PF1022A and emodepside are active against animal nematodes by interaction with the latrophilin receptor. These receptors regulate the release of neurotransmitters, such as amines and neuropeptides[1]. Emodepside acts at the

[1] Willson, J, *et al*, (2003) The effect of the anthelmintic emodepside at the neuromuscular junction of the parasitic nematode *Ascaris suum*. Parasitology (2003), 126, 79-86.

neuromuscular junction by stimulating presynaptic receptors belonging to the secretin receptor family, resulting in paralysis and death of the parasite[2], however the exact cellular mechanism is unknown. Emodepside is active against ascarids and hookworms. Emodepside has not previously been considered for scheduling by the NDPSC.

Praziquantel is an anthelmintic drug and is used as an antiparasitic agent in humans and animals. It is included in Schedule 4 for human therapeutic use, but is unscheduled for animal use. The ADI of praziquantel is 0.02 mg/kg/day, based on a NOEL of 20 mg/kg/day in a subchronic dog study

DISCUSSION

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

[Section deleted].

Praziquantel for animal use is currently not listed in the SUSDP. It was listed in Appendix B but the Committee recalled that this entry was deleted in 1989. The Committee in 1995 had considered that prazinquantel for animal use remain unscheduled on the basis of its low toxicity.

Data previously evaluated indicated that the acute oral toxicity of praziquantel was very low (LD_{50} 2840 in rats). Toxic signs were indicative of central nervous system effects, mainly sedation. Praziquantel was not a skin irritant (after single and 3 week administration) or an eye irritant in rabbits. It was also not a skin sensitizer in guinea pigs.

The Committee considered the appropriateness of including praziquantel in Appendix B of the SUSDP. As there were a number of registered veterinary products containing praziquantel, the Committee agreed that it should first obtain from the APVMA, details of registered products, their approved use-patterns and overall label instructions and also details of whether there had been any adverse effects arising from use. The results of a literature review of possible adverse effects arising from the use of praziquantel in veterinary use was also requested from the APVMA.

The Committee also requested the Secretariat to research the background to the existing Schedule 4 entry for praziquantel. Further consideration of the scheduling of praziquantel was therefore deferred until the October 2005 meeting.

[2] EMEA (2005). Committee for Medicinal Products for Veterinary Use: Summary of opinion for Profender. 9 March 2005.

DECISION 2005/44 - 12

The Committee agreed that, on the basis of its toxicity profile, emodepside for veterinary use be included in Schedule 6 of the SUSDP with a cut-off to Schedule 5 at 2.5 per cent or less to accommodate the product.

Schedule 6 – New Entry

EMODEPSIDE for the treatment of animals except when included in Schedule 5.

Schedule 5 – New entry

EMODEPSIDE in preparations for external treatment of animals containing 2.5 per cent or less of emodepside.

6.2 MILBEMECTIN

PURPOSE

The Committee considered the scheduling of the new pesticide milbemectin.

BACKGROUND

XXXXXXXX submitted data in support of the approval of a new active ingredient, milbemectin, and the registration of the new product XXXXXXXX, containing XXXXXXXX at XXX g/L. The product is proposed to be used for the XXXXXXXX. The applicant had also requested the consideration of scheduling for milbemectin and the establishment of an ADI and ARfD.

Milbemectin is a member of the mectin class of insecticides/acaricides. The target for milbemectin is the γ-aminobutyric acid (GABA) receptor in the peripheral nervous system. The compound stimulates the release of GABA from nerve endings and enhances the binding of GABA to receptor sites on the post-synaptic membrane of inhibitory motor neurons of mites and other arthropods. This enhanced GABA binding results in an increased flow of chloride ions into the cell, with consequent hyperpolarization and elimination of signal transduction, resulting in an inhibition of neurotransmission.

Milbemectin has been registered overseas for use as an insecticide in many crops including fruits, melon, vegetable and ornamentals. Several similar compounds, such as abamectin, ivermectin and milbemycin oxime, have been registered in Australia.

DISCUSSION

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

[Section deleted].

Based on the toxicological hazard of milbemectin, the Committee noted that the OCS had suggested that the NDPSC consider milbemectin appropriate for inclusion in Schedule 6 of the SUSDP with an appropriate cut-off to Schedule 5 for the product containing 1% or less milbemectin. The formulated product was a moderate eye irritant which was consistent with a Schedule 5 classification. The Committee agreed with this proposal.

DECISION 2005/44 - 13

The Committee agreed that, on the basis of its toxicological profile, milbemectin be included in Schedule 6 of the SUSDP with a cut-off to Schedule 5 in preparations containing 1 per cent or less to accommodate product.

Schedule 6 – New entry

MILBEMECTIN **except** when included in Schedule 5.

Schedule 5 – New Entry

MILBEMECTIN in preparations containing 1 per cent or less of milbemectin.

6.3 PINOXADEN

PURPOSE

The Committee considered the scheduling of pinoxaden, a new herbicide for the XXXXXXXX.

BACKGROUND

XXXXXXXX applied for the approval of pinoxaden and registration of Axial XXXXXXXX for use in the XXXXXXXX. The product will contain XXX g/L pinoxaden and XXX g/L cloquintocet-mexyl as the active ingredients in a formulation containing hydrocarbon solvent.

Cloquintocet-mexyl is a herbicide safener and is listed in Schedule 5 of the SUSDP.

Pinoxaden is not currently included in the SUSDP and no first-aid instructions have been established. Toxicological data have been evaluated previously for an application for a field trial permit. Further toxicological data have now been supplied to support the approval of pinoxaden and registration of the new product.

DISCUSSION

Pinoxaden is a member of the new phenylpyrazoline class of herbicides and its herbicidal mode of action is yet to be elucidated.

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

[Section deleted].

Based on its acute toxicological profile, in particular its severe eye irritancy, the OCS review recommended that it would be appropriate to include pinoxaden in Schedule 6 of the SUSDP. However, the Committee noted that the product had only moderately acute toxicity. Consequently, a cut-off of 10 per cent to Schedule 5 was considered appropriate for the product.

DECISION 2005/44 - 14

The Committee agreed that on the basis of the toxicological profile for pinoxaden and noting severe eye irritancy, pinoxaden be included in Schedule 6 of the SUSDP. The Committee further agreed that on the basis of moderate toxicity, in particular moderate eye irritancy, for the product, a cut-off to Schedule 5 for preparations containing 10 per cent or less was appropriate.

Schedule 6 – New entry

PINOXADEN **except** when included in Schedule 5.

Schedule 5 – New Entry

PINOXADEN in preparations containing 10 per cent or less of pinoxaden.

6.4 PROTHIOCONAZOLE

PURPOSE

The Committee considered the scheduling of a new active ingredient, prothioconazole.

BACKGROUND

XXXXXXXX applied for approval of the active constituent prothioconazole and registration of the product XXXXXXXX, a water-based flowable concentrate for seed treatment (FS) formulation containing XXX g/L prothioconazole, a triazole compound for XXXXXXXX. The treatment of cereal seed is only for subsequent crop planting.

The product is formulated in XXXXXXXX and will be imported into Australia fully labelled for distribution. It will be packaged in XXX L High Density Polyethylene containers. A formulation of prothioconazole designed for foliar application to cereals is registered in Germany (XXXXXXXX). XXXXXXXX (XXXXXXXX) has recently been approved for seed treatment use in the UK.

Extensive toxicological data had been supplied in supporting the approval of prothioconazole and registration of a new product.

The OCS made use of the UK prothioconazole evaluation which covered most of the data submitted to Australia by XXXXXXXX, although considerable editorial changes, and some changes in interpretation, had been made to suit Australian requirements.

DISCUSSION

The Committee noted that:

- 20 chemicals in this class (triazole fungicides) had been previously scheduled; 16 of them (bromuconazole, cyproconazole, diclobutrazol, difenoconazole, diniconazole, epoxiconazole, fenbuconazole, hexaconazole, myclobutanil, penconazole, propiconazole, tebuconazole, tetraconazole, triadimefon, triadimenol, and triticonazole) were classified in Schedule 5 and four of them (azaconazole, fluquinconazole, flusilazole, and flutriafol) were classified in Schedule 6.

- prothioconazole shared similar acute toxicity profile (low oral, dermal, and inhalation toxicity, with only slight eye or skin irritation) with most of other chemicals in this class. Prothioconazole had been assessed by OCS as:

[Section deleted].

- The acute toxicity of XXXXXXXX (XXX g/L prothioconazole) was summarised by OCS as:

[Section deleted].

The Committee noted that the toxicological profile of prothioconazole appeared to be a little different from other triazole fungicides previously considered by the Committee over many years and which, based upon their toxicological profiles had been classified as Schedule 5 or Schedule 6. Priothioconazole presented a different toxicological picture and though conscious of the Schedule 5 and Schedule 6 classification of other substances in the class, justified in the view of the Committee, the substance being exempted from scheduling.

The Committee agreed that the OCS should be asked to tabulate all the triazole fungicides against their toxicological differences and their respective schedule classification and to present that to the Committee at its next meeting if necessary.

DECISION 2005/44 - 15

The Committee agreed with the assessment of the OCS and, having regard to the overall toxicological profile of prothioconazole, agreed to exempt prothioconazole from scheduling through its inclusion in Appendix B of the SUSDP.

Appendix B – New Entry

	Date of Entry	Reason for Listing	Area of Use
PROTHIOCONAZOLE	June 2005	a	1.3.1

6.5 IMIDAPRIL

PURPOSE

The Committee considered the scheduling of imidapril.

BACKGROUND

XXXXXXXX submitted an extensive toxicology data package in support of approval of a new active constituent, imidapril hydrochloride, and the registration of three new products, XXXXXXXX, XXXXXXXX and XXXXXXXX containing imidapril hydrochloride. Imidapril hydrochloride (imidapril, TA-6366; hereafter referred to as imidapril) is a long-acting, non-sulfahydril pro-drug, which is hydrolysed to form an active metabolite, imidaprilat, an agiotensin-converting enzyme (ACE) inhibitor. The product is proposed to be used for the treatment of XXXXXXXX.

Although registration of imidapril for veterinary use is being sought for the first time, ACE inhibitory active constituents such as enalapril, lisinopril and ramipril have been registered for human use in Australia, and are listed in Schedule 4 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

DISCUSSION

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

[Section deleted].

Based on its intended use as a therapeutic agent requiring professional veterinary advice and management prior to use, the OCS suggested that Schedule 4 of the SUSDP was appropriate for imidapril hydrochloride. The Committee agreed with this proposal.

DECISION 2005 - 16

The Committee agreed to the inclusion of imidapril hydrochloride in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate veterinary diagnosis and that the safe use of the medicine required management and monitoring by a veterinary professional.

Schedule 4 – New entry

IMIDAPRIL.

6.6 AMINOPYRALID

PURPOSE

The Committee considered the scheduling of a new active ingredient aminopyralid.

BACKGROUND

XXXXXXXX applied for the registration of XXXXXXXX, an emulsion, oil in water, formulation containing XXX g/L of the new active ingredient aminopyralid, present as the triisopropanolamine salt, and XXX g/L fluroxypyr, present as the methylheptyl ester. As part of this application for the registration of XXXXXXXX, approval was also sought for the new active constituent aminopyralid. Fluroxypyr as the methylheptyl ester is present in the already registered product XXXXXXXX. Fluroxypyr is included in Appendix B of the SUSDP.

DISCUSSION

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

[Section deleted].

The Committee considered that the severe eye irritancy of XXXXXXXX may be related to the presence of aminopyralid, despite its relatively low concentration in this product. The other active ingredient in XXXXXXXX, fluroxypyr, was only a slight eye irritant. However the presence of XXXXXXXX as a solvent (approximately XXX % of the formulation) together with a surfactant undoubtedly contributed to the severe eye irritancy of the XXXXXXXX formulation. The eye irritancy of aminopyralid was the

principal factor lead to it being placed in Schedule 6. The company had not provided any data to support a cut-off to a lower schedule.

DECISION 2005/44 - 17

The Committee agreed that based on the assessment of toxicity and having regard to severe eye irritancy, aminopyralid be included in schedule 6 of the SUSDP.

Schedule 6 – New entry

AMINOPYRALID.

6.7 HALOFUGINONE

PURPOSE

The Committee considered the scheduling of halofuginone in dilute preparations.

BACKGROUND

XXXXXXXX applied for the registration of XXXXXXXX, containing XXX g/L halofuginone base (as lactate salt) as the active constituent. The product is intended for use as an oral solution for the prevention and treatment of diarrhoea and scours in calves caused by *Cryptosporidium parvum*. At the time of the meeting there were no registered products containing halofuginone in Australia. An APVMA Permit for the use of XXXXXXXX as an oral solution for the prevention and treatment of diarrhoea and scours in calves caused by *Cryptosporidium parvum* expired on XXXXXXXX. XXXXXXXX provided supplementary toxicity data.

Halofuginone belongs to the quinazolone group of chemicals and is a synthetic derivative of febrifugine. The *trans* isomer of halofuginone is the active compound (oral LD_{50} = 4-5 mg/kg bw in mice), while the *cis*-isomer is considered to be an impurity (oral LD_{50} = 342-367 mg/kg bw in mice). On the basis of its acute toxicity, halofuginone, except in prepared stockfeeds containing 3 g/tonne or less of halofuginone, is in Schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), with an Appendix J rider. The applicant initially requested consideration of a Schedule 5 entry for halofuginone to accommodate this particular product but later amended this to a Schedule 4 request.

DISCUSSION

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

[Section deleted].

DECISION 2005/44 - 18

The Committeee agreed that it would be appropriate for preparations containing 0.1 per cent or less of halofuginone for the treatment of *Cryptosporidium* infections in calves to be included in Schedule 4 of the SUSDP as diagnosis and treatment requires veterinary management. Noting that there are no registered halofuginone products and therefore no stockfeeds containing halofuginone in the marketplace, the Committee further agreed to amend the Schedule 7 entry for halofuginone to remove reference to stockfeeds.

Schedule 4 – New entry

HALOFUGINONE in preparations containing 0.1 per cent or less of halofuginone for the treatment of animals.

Schedule 7 – Amendment

HALOFUGINONE – amend entry to read:

HALOFUGINONE **except** when included in Schedule 4.

6.8 PARAQUAT

PURPOSE

The Committee reconsidered the scheduling of paraquat XXXXXXXX.

BACKGROUND

XXXXXXXX had applied for the registration of XXXXXXXX containing XXX g/L paraquat dichloride as the active constituent. This new formulation was based on XXXXXXXX. [3 Sentences deleted].

The product would be diluted in water and applied as a spray (mainly via a boom) to control weeds in broadacre crops and pastures (low volume application) or to hops, orchards, bananas, vineyards, potatoes, sugarcane, peanuts, vegetables, firebreaks and non-crop situations (high volume application). For low volume applications, the product would be applied in 50-200 L water/ha, while for high volume applications it would be applied in 250-400 L water/ha. The applicant had indicated its intent for the aerial application of this product, with the draft product label recommending it be applied in 30-60 L of water/ha. The draft product label recommended a spray quality in the fine to medium range (droplet size of 200-250 μm) for all applications.

The applicant requested a consideration of the scheduling of this formulation of paraquat. Paraquat is listed in Schedule 7 of the SUSDP with no cut-off to lower schedules. Paraquat was only recently (2004) the subject of a review conducted by the Office of

Chemical Safety (OCS) under the auspices of the Australian Pesticides and Veterinary Medicines Authority's (APVMA) chemical review program. The poisons schedule for paraquat was re-examined during this time and considered to be appropriate.

DISCUSSION

In support of product registration, XXXXXXXX provided the standard set of toxicity studies conducted in laboratory animals which were assessed by the OCS.

The Committee noted the OCS Health Assessment Technical Report, which specifically addressed the toxicological and critical public health issues associated with XXXXXXXX, including a consideration of the poison schedule classification for paraquat.

The report indicated that a significant feature of XXXXXXXX was its XXXXXXXX, which was claimed to reduce oral poisoning incidents (accidental or deliberate). [3 Sentences deleted]. The intended outcome is the removal of a proportion (reportedly most) of an ingested oral dose. Therefore, the anticipated increase in safety of XXXXXXXX relative to the existing paraquat product (that is marketed by XXXXXXXX) relies predominantly on the improved efficacy of the XXXXXXXX to remove a significant proportion of an ingested paraquat dose from the stomach.

When the NDPSC first considered paraquat in 1964, it was placed in S6 based on its acute toxicity profile. In 1972, paraquat was placed into S7 because of its unique toxicity insofar as its acute toxicity appeared to be secondary to its capacity to cause mortality. In 1977, the committee agreed to the inclusion of the XXXX in all liquid paraquat formulations as it was felt this was a unique one-off situation, where inclusion of the emetic would be beneficial. However, in 1987, this requirement was removed based on information indicating that the emetic was ineffective in preventing deaths - instead it was decided that liquid paraquat preparations should contain a coloured blue or green dye and a stenching agent. In addition, paraquat was to be removed from the domestic market.

The studies submitted indicated that XXXXXXXX has [sentence deleted]. Based on these data, the acute toxicity profile of XXXXXXXX is consistent with the known toxicity profile of paraquat. The Committee noted that paraquat dichloride (the commercially available paraquat salt) is usually supplied to product formulators as a 'manufacturing concentrate', which contains 320-425 g/kg of paraquat ion (ie. 442 to 587 g/kg paraquat dichloride). XXXXXXXX contains XXX g/L (XXX g/kg) paraquat ion, which is approximately XXX% of the 'manufacturing concentrate'. Therefore the concentration of paraquat in the product is XXXXXXXX than the concentration found in the manufacturing concentrate.

In support of the improved safety of the new XXXXXXXX formulation, two toxicokinetic studies conducted in dogs were also submitted. Only one of these was conducted using a formulation equivalent to the product intended for marketing in Australia. XXXXXXXX had indicated that the dog is the best animal model to test the

improved safety of the new XXXXXXXX formulation because, like humans, they are a vomiting species and are particularly sensitive to paraquat toxicity. XXXXXXXX also claimed that the absorption of paraquat into the blood stream is best represented by the dog model.

In the main study, dogs were [section deleted].

In the second study conducted on an XXXXXXXX formulation not equivalent to the product intended for marketing in Australia, similar results were obtained. This study found that [section deleted].

As the only evidence to support the improved safety of the new XXXXXXXX formulation, the committee noted that the dog studies had a number of shortcomings:

- only three dogs were tested;
- no control dog was included in the study;
- there was no pathology conducted at the lower doses and therefore it was unclear whether lung lesions had occurred and then subsequently resolved;
- the benefit of the XXXXXXXX was unclear because the concentration of the XXXXXXXX was actually XXX-fold higher than standard XXXXXXXX – ie there was no direct experimental comparison of the old and new formulation

The Committee was informed that following discussions with the OCS, XXXXXXXX had provided just prior to the NDPSC meeting, some summary data (and also raw data) to highlight the benefit of the XXXXXXXX. On face value, this data confirmed that the presence of the XXXXXXXX reduces plasma levels of paraquat in dogs. Additional summary data also suggested that XXXXXXXX reduces absorption of paraquat across isolated rat gastrointestinal tract.

The Committee noted a number of other issues raised in the OCS report that argued against a cutoff for paraquat into a lower schedule such as the lack of an effective antidote or treatment for paraquat poisoning and the potential for paraquat to enter the homegarden market. In addition, there is doubt surrounding the clinical benefit of inducing emesis in the event of accidental poisoning. The NDPSC had previously concluded that the XXXXX in paraquat formulations XXXXX was ineffective in preventing deaths. Further, in 2000 the NDPSC initiated a Working Party to review the first-aid instructions for pesticide products with the view to ensuring that they reflected best clinical practice. The outcome of this review was that the first-aid instruction to induce vomiting in the event of accidental poisoning is no longer considered appropriate for any pesticide product.

The Committee noted that the OCS supported the registration of XXXXXXXX but could find no grounds to recommend that paraquat have a cut-off into Schedule 6 of the SUSDP. This position was based on: (1) The intrinsic toxicity of paraquat in XXXXXXXX remains unchanged and the clinical benefit of inducing emesis (vomiting) for accidental poisonings is doubtful; (2) There is no effective antidote or treatment for

paraquat poisoning; and (3) Paraquat products are considered too hazardous for home garden use and therefore it would be inappropriate for paraquat to be included in Schedule 6 of the SUSDP

To address the concern over potential homegarden use of the new formulation if there were to be a cutoff for paraquat into Schedule 6, XXXXXXXX had suggested a number of risk mitigation measures:

- XXXXXXXX would only be sold through accredited and licensed agricultural resellers;

- The following statement could be included on the product label

> "FOR USE ONLY AS AN AGRICULTURAL HERBICIDE. THIS PRODUCT IS TOO HAZARDOUS TO BE USED IN THE HOMEGARDEN"

- Restrict the formulation to closed system packaging only.

The Position of XXXXXXXX

The Committee gave careful and detailed consideration to the position of the applicant, XXXXXXXX. The Committee was advised that XXXXXX had been given the opportunity to review the Office of Chemical Safety's Draft Health Assessment Technical Report and to discuss on several occasions, the toxicological and related public health issues with representatives of the OCS. XXXXXXXX's position was set out in letters of 12th, 13th and 24th May 2005 and 17th June 2005 which were made available to the Committee.

The Committee noted that in their letter of 12 May 2005, XXXXXXXX had made the following points in arguing that a S6 classification was appropriate:

- Scheduling this product as S6 rather than S7 is vital to its acceptance to signify that it is a breakthrough in formulation technology that provides significant safety benefits to the user.

- Although toxicologically-significant absorption occured at high doses of the new XXXXXXXX formulation, the 16-times safening will increase significantly the survival rate following oral ingestion.

- Although the LD_{50} in the rat is not greatly improved with the new formulation, its acute toxicity profile is consistent with that of a schedule 6 poison.

- The lack of an effective antidote for paraquat poisoning is insufficient grounds for an agricultural chemical to be a Schedule 7 poison. In addition, and quite apart

from the preventative effects of XXXXXXXX (which has an antidote function to some extent), there are mechanical antidotes to paraquat poisoning by oral ingestion that can be used to prevent absorption through the gut.

- XXXXXXXX is very clearly intended as an agricultural and horticultural herbicide as it is only sold through agricultural suppliers and the smallest pack size of XXX litres cannot be considered a homegarden pack size. In addition, this product would only be sold to users with training and accreditation in the use and application of agricultural chemicals. XXXXXXXX is happy for a statement such as "NOT TO BE USED IN THE HOME GARDEN" to be included on the product label as is currently the case for paraquat products if required, or for this to be included as a condition in the SUSDP.

- If XXXXXXXX shared this technology with third party suppliers it would be under the condition that the product only be sold for agricultural and horticultural use, and not for use in the homegarden.

The Committee further noted that in a subsequent letter of 13th May 2005, XXXXXXXX made further comment on:

- the toxicokinetic studies that were conducted on dogs and the proper interpretation of the results in assessing risk in the case of oral ingestion of paraquat with XXXXXX,
- the availability of an antidote/treatment for paraquat poisoning, and
- limitations on public access to substances scheduled as S6, rather that S7

On 24th May, XXXXXXXX provided further comment, particularly in respect to the draft OCS Health Assessment Technical Report. XXXXXXXX stated that the value of an XXXXXXXX as a co-formulant within XXXXXXXX is essential to its' safening mechanism, resulting in an early emesis. This is quite different to the administration of an emetic after the event (and sometimes some hours after) as a first aid measure. XXXXXXXX believes the data has demonstrated a benefit from the XXXXXXXX technology in significantly reducing toxicity in the dog.

In correspondence of the 17th June 2005, XXXXXXXX reaffirmed its intention not to sell into the home-garden market and to ensure product labels reflected this. XXXXXXXX also provided the details of closed system packaging of XXX and XXX litres which they were prepared to introduce to mitigate against accidental poisoning and the possibility of product being diverted into the home-garden market.

Public Submissions in Response to the Pre-Meeting Gazette Notice

In response to the pre-meeting Gazette Notice, submissions were received from:

- XXXXXXXX

- XXXXXXXX.
- XXXXXXXX.
- XXXXXXXX
- XXXXXXXX
- XXXXXXXX
- XXXXXXXX

XXXXXXXX noted that there was reluctance within the farming community to use Schedule 7 agricultural chemicals. This had resulted in paraquat and paraquat-based products becoming "last-bet" options within the broadacre farming community as the alternative glyphosate knockdown products were deemed to be relatively safe. This concern over the use of Schedule 7 products was limiting use of paraquat alone and in conjunction with other materials despite paraquat having a clear technical advantage when rapid knockdown capability was required. XXXXXXXX further noted that this issue was of enormous importance to Western Australia where direct drill/minimum tillage systems of cropping were now the norm. The first step to a successful outcome of such systems was highly efficient weed knockdown capabilities that required the support of both paraquat and glyphosate. The submission also noted Sub Section 52E(1)(f) of the *Therapeutic Goods Act 1989* which states 'the need to access a substance, taking into account its toxicity compared with other substances available for a similar purpose". Similar comments to those made by XXXXXXXX were also made by XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX.

XXXXXXXX made similar comments to XXXXXXXX. XXXXXXXX stated that there was perceptual and logistical barriers to the use of Schedule 7 products and that there was a need for alternative herbicides to minimize resistance to glyphosate. XXXXXXXX therefore supported the availability of the new formulation of paraquat as a Schedule 6 product.

XXXXXXXX noted that the availability of a paraquat-based product in Schedule 6 had the potential to increase weed management and cropping systems sustainability in Australian agriculture and reduce the future cost of glyphosate resistance in Australian farming.

XXXXXXXX's public submission of 25th May 2005, reiterated the points made in correspondence to the OCS. In particular, XXXXXXXX noted that:

- Paraquat is a unique contributor to sustainable development in agriculture as it is used extensively as a knock-down herbicide prior to planting of broadacre crops as an alternative to traditional cultivation methods. This practice minimizes soil erosion and helps to retain soil moisture.

- The use of paraquat in rotation with glyphosate would help to avoid the development of glyphosate resistance.

- There is no intention for XXXXXXXX to be sold for home garden use. Sales of the product and any other brand names of the same formulation licensed by XXXXXX to third parties would only be through agricultural and rural suppliers to bonafide agricultural, horticultural and viticultural users. If the NDPSC considers it necessary to further restrict access to the public to this product, it may be an option to sell it only in large volume closed system packaging.

- [Paragraph deleted].

- The toxicology data submitted to the OCS supports a Schedule 6 poisons classification. A Schedule 6 classification is essential to differentiate it from standard paraquat and to encourage farmers to adopt it for herbicide resistance management.

- XXXXXXXX should be considered under sub Section 52E(1) (f) of the Therapeutic Goods Act viz "the need to access a substance, taking into account its toxicity compared with other substances available for a similar purpose" as there are no real cost-effective alternatives available.

- There are many examples of multiple schedule entries for agricultural chemicals depending on formulation strength eg abamectin, emamectin, diquat and/or formulation type eg lambda-cyhalothrin, deltamethrin, endosulfan and aparathion-methyl. XXXXXXXX suggests that paraquat now be scheduled according to formulation type as well, using the following suggested wording *"Paraquat in AC preparations containing 250g/L or less paraquat dichloride plus* XXXXXXXX *and* XXXXXXXX *in closed system packaging of x litres or more"*

- The current Schedule 7 classification reflects the situation with paraquat as it existed 20 years ago. This unique formulation delivers a new standard in human safety for paraquat formulations offering an ideal stewardship opportunity for XXXXXXXX and government regulators alike to promote safer pesticide use.

While the Committee agreed that the new formulation did appear to be a "safer" formulation, members were concerned with the overall lack of supporting data, in particular, the inadequacy of the dog study to further explore lung toxicity at lower doses. In this regard, the Committee was of the view that the dog study should have looked at whether repeated exposures caused lung damage, including exposure at lower doses with accompanying histopathology. The Committee was also concerned that there was no data on human exposure to the XXXXXXXX, particularly as its use was 3X that used in the past. The impact such a dose might have on uncontrolled vomiting and in the emergency management of poisoning cases eg lavage had also not been pursued.

The Committee also requested that data be provided that demonstrated the benefit of the XXXXXXXX formulation, including human data if available. If possible, data which

compared the "old" and new XXXXXXXX formulation would be particularly useful. All data should be complete study reports and not summaries or in-house reviews.

Concern was also expressed that there was a possibility that a change of scheduling of paraquat, ie to Schedule 6, would allow diversion to the home garden market or an increased opportunity for paraquat to be implicated in suicide poisonings. The Committee noted that in Australia, suicide poisonings involving paraquat were approximately 4-5 per year and agreed that the frequency of such was unlikely to be influenced by the new paraquat formulation. In regard to occupational poisonings involving paraquat, the incidence was also very low. This could be attributed to several reasons including the strict regulatory controls that had existed over many years, particularly those linked to the Schedule 7 classification. A relaxation of those controls presented a possible risk that occupational exposure could increase. Given the public health implications arising from paraquat poisoning, any increase in poisoning cases, should they occur, would be untenable. However, the Committee did acknowledge that the new formulation offered advantage in that accidental exposure, should it occur, may result only in lung damage rather than death. The Committee also noted XXXXXXXX's proposal to market the formulation in no less that XXX litre drums or alternatively, to only market the formulation in a closed system which would help to reduce the possibility of both user exposure and diversion into the home garden market or other markets where use was not permitted. This was seen as a positive step towards the mitigation of the risks involved in the use of paraquat.

The importance to agriculture in being able to use paraquat in place of glyphosate and thereby minimise glyphosate resistance was also noted and appreciated.

OUTCOME

The Committee agreed that, because of its concern in respect to:

- the adequacy of the dog study, (including the lack of follow up at lower doses),
- the absence of data on the XXXXXXXX, particularly in relation to its use at 3X previous doses and the likely effect on humans, and
- the absence of data comparing the XXXXXXXX formulation with the existing formulation,

the current scheduling of paraquat remained appropriate.

The Committee indicated that it would be prepared to reconsider the matter following the assessment of further information that addressed these concerns. The Committee also requested the XXXXXXXX member to ensure that the APVMA accorded priority to any further paraquat scheduling submission from XXXXXXXX.

6.9 DICHLOBENIL

PURPOSE

The Committee considered the scheduling of the herbicide dichlobenil.

BACKGROUND

The active constituent dichlobenil is a non-selective organochloride herbicide belonging to the nitrile group of herbicides. It is a systemic herbicide, and mediates its activity via inhibition of cellulose synthesis in actively growing plant tissue.

Dichlobenil (in the product XXXXXXXX) is intended for the control of XXXXXXXX. The amount of the product to be used depends on the XXXXXXXX and the size of the XXXXXXXX. The label directions advise to empty the contents in a package into a pail or bucket and mix the two components thoroughly before pouring the final mix directly into XXXXXXXX. According to the label, mixing can also be done by shaking the package vigorously after removal of the plastic tie in the middle of the bag which separates the two dry chemical components.

Dichlobenil has been registered in Australia since 1971 and based on the toxicology data available at that time it was exempted from scheduling and included in the Appendix B of the SUSDP. However, because there was no clear rationale given for this classification, dichlobenil was removed from Appendix B in 1998. The present evaluation reconsidered the currently available toxicology data for dichlobenil for re-classification of this chemical in the SUSDP.

DISCUSSION

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

[Section deleted].

Based on its moderate acute oral toxicity in guinea pigs and rabbits, moderate dermal toxicity in rabbits, observed liver, kidney and thyroid effects, the OCS suggested that the NDPSC may wish to consider Schedule 6 as appropriate for dichlobenil, in order to reinstate this chemical in the SUSDP. No data was presented on which to consider a cut-off to Schedule 5.

The Committee noted that there were 5 registered products listed on the APVMA's PUBCRIS database. The adoption of a Schedule 6 classification for dichlobenil would impact on 3 products which were currently listed as being exempt from scheduling. The remaining 2 products were indicated to already have a Schedule 6 poisons classification as a result of other active ingredients.

The APVMA representative confirmed that all registrants of products containing dichlobenil would be advised of the decision to change the scheduling status of dichlobenil.

As the Committee's decision could impact upon a range of products, the Committee indicated its willingness to consider comment from product registrants if they were received by the closing date for further public submissions.

DECISION 2005/44 - 19

The Committee agreed that the moderate acute oral toxicity and dermal toxicity warranted the inclusion of dichlobenil in Schedule 6 of the SUSDP.

Schedule 6 – New entry

DICHLOBENIL.

6.10 SPINOSAD

PURPOSE

The Committee considered the scheduling of spinosad.

BACKGROUND

XXXXXXXX applied for registration of a new product XXXXXXXX, a XXXXXXXX formulation containing XXX g/L spinosad as the active ingredient. The product is for the XXXXXXXX. The applicant requested exemption from scheduling for XXXXXXXX based on submitted toxicology data.

Spinosad, which possesses insecticidal activity, is a fermentation product of the bacterium *Saccharopolyspora spinosa*. Spinosad consists of approximately 10 related chemicals, of which two closely related compounds, spinosyn A and spinosyn D, account for about 88% of the spinosad activity.

Spinosad is currently included in Schedule 5 of the SUSDP, except in aqueous suspensions containing 12% or less of spinosad, which are exempt from scheduling. With this application, the NDPSC was requested to reconsider the existing scheduling cut-off for spinosad.

DISCUSSION

The active ingredient, spinosad is currently included in Schedule 5 of the SUSDP, except in aqueous suspensions containing 12% or less of spinosad, which are exempt from scheduling.

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

[Section deleted].

The APVMA PUBCRIS data base listed 8 registered products in Australia containing spinosad at concentrations from 1 per cent to 80 per cent. The impact of setting a cut-off at 25% or less would be minimal with one product containing 12.5 per cent becoming exempt from scheduling.

DECISION 2005/44 - 20

The Committee agreed that, based on the low acute toxicity of spinosad, the cut-off for exemption from scheduling for spinosad be amended to 25 per cent or less.

Schedule 5 – Amendment

SPINOSAD – Amend the entry to read:

SPINOSAD **except** in aqueous suspensions containing 25 per cent or less of spinosad.

6.11 TRIBUTYLTIN OXIDE (TBTO) AND TRICLOSAN

PURPOSE

The Committee considered the scheduling of tributyltin oxide (TBTO) and triclosan.

BACKGROUND

The Committee noted that XXXXXXXX had applied for the registration of a new product, XXXXXXXX, containing XXX g/L tributyltin oxide (TBTO) and XXX g/L triclosan. The product is for the XXXXXXXX. Tributyltin oxide is currently in Schedule 7 of the SUSDP. No change in scheduling of TBTO is proposed.

It was noted that triclosan was originally exempted from the requirements of scheduling but was not included in Appendix B (ie. compounds of low toxicity not requiring control by scheduling) when it was reinstated. A change to the scheduling of triclosan was proposed.

DISCUSSION

Tributyltin oxide

It was noted that tributyltin oxide was currently included in the Schedule 7 of the SUSDP for organotin compounds with no exception that relates to treated textiles. The product,

XXXXXXXX has low acute oral and dermal toxicity, is a moderate skin irritant and is corrosive to the eyes of rabbits.

A cut-off to a less restrictive schedule was not proposed for tributyltin in this product.

Triclosan

The Committee recalled that some years ago, triclosan was exempted from the requirements of scheduling, but it was subsequently removed from Appendix B.

Triclosan has low acute oral toxicity with an LD_{50} >4000 mg/kg, but there is an enormous difference between oral and i.v. (rat i.v. LD_{50} 29 mg/kg), suggesting some potential for systemic toxicity if adequate blood levels can be achieved.

Acute inhalation toxicity of triclosan aerosol was low and no clinical signs of toxicity were observed. The LC_{50} was greater than 283 mg/m^3.

Triclosan is a slight/moderate eye irritant, but is not a skin sensitiser. At concentrations less than 10%, triclosan is not a primary skin irritant.

In development studies in rabbits, effects on the foetus, such as decreased litter and pup weight and increased supernumerary ribs were seen only in rabbits given severely maternotoxic doses. No reproduction studies were submitted. Genotoxicity studies showed negative results.

Based on the available information, the OCS recommended that the NDPSC consider triclosan for inclusion in Schedule 5 of the SUSDP with a cut-off (ie. exempt from poison scheduling) for products containing 10% or less of triclosan, to accommodate existing antibacterial products which are available on the Australian market.

The Committee noted that pesticide and veterinary chemical products containing triclosan were listed in the APVMA's PUBCRIS data base. The maximum concentration in products was 0.5 percent. Pharmaceutical products were listed on the ARTG. The maximum concentration in products was 1 percent. It was unknown what the triclosan concentration might be in individual consumer products but NICNAS advice was that it would generally be less than 1% and therefore unlikely to exceed the proposed cut-off level of 10 percent which had been proposed to accommodate existing products in the marketplace.

NICNAS also advised that it is currently undertaking a PEC review of triclosan and substantial health and environmental data had been provided by importers of the chemical and products containing the chemical. The data is currently being assessed by NICNAS. One of the reasons for declaration of the chemical for PEC review was the potential for bioaccumulation and persistence. NICNAS has commissioned a consultancy to estimate triclosan in breast milk samples which is likely to be completed in September 2005. The

information from this consultancy will feed into the report and a draft report is likely to be completed by end 2005.

It was also noted that NICNAS will also review the OCS toxicology assessment report to ascertain if all the data has been provided and is available for consideration, including by the NDPSC. NICNAS suggested that if a scheduling decision was made at the June 2005 NDPSC meeting, it was possible that triclosan may need rescheduling on completion of the NICNAS review. NICNAS further suggested that scheduling be considered specifically for the APVMA-referred product or the Committee could foreshadow at the next meeting that scheduling would be considered at the end of the NICNAS review. However this would delay a timely response to the APVMA.

Public Submissions

In response to the pre-meeting Gazette Notice, XXXXXXXX advised that it wished to reserve the right to comment pending disclosure of further information in the Minutes of the June meeting.

The Committee noted that comments on the proposal, specifically in respect to triclosan, were received from:

- XXXXXXXX noting that NICNAS was currently reviewing triclosan and that it might therefore be appropriate to defer consideration of scheduling until the NICNAS review had been completed. XXXXXXXX requested that it be advised of the outcome and have the opportunity for further submission if appropriate.

- XXXXXXXX highlighted a number of registered therapeutic goods containing triclosan and requested that the Committee give consideration to them when making a scheduling decision for triclosan. All the XXXXXXXX contained 1% or less of triclosan.

- XXXXXXXX suggesting that the scheduling of triclosan be deferred until the NICNAS PEC review is completed. XXXXXXXX wished to be informed of the outcome of the Committee's deliberations.

- XXXXXXXX noting the NICNAS PEC review and suggesting that scheduling considerations be deferred until the review was completed and released.

- XXXXXXXX which made no specific comment but reserved the right to comment during the post-meeting period.

- XXXXXXXX who identified an interest in triclosan and reserved the right to make comment in the post-meeting period.

The Committee agreed that it would be beneficial to have the benefit of the comprehensive NICNAS review before making further recommendations about the

scheduling of triclosan and appropriate cut-off levels. Of particular interest to the Committee would be the assessment of potential eye and skin irritancy.

The Committee noted that in respect to the product XXXXXXXX, investigations of possible human exposure from fabrics treated with the product had been provided. However, in the broader context, the question was raised as to the possible need to consider the scheduling of products containing, or treated with Schedule 7 products, such as fabrics, clothing and paper. Treated products, particularly those treated with Schedule 7 products were not captured by the scheduling system or on occasion by the various regulatory systems. While this issue had been addressed in the past, the Committee agreed that it was appropriate to again consider the issue of treated products. The XXXXXXXX member agreed to provide a discussion paper addressing Schedule 7-treated products and their residues to the October 2005 meeting of the NDPSC.

OUTCOME

The Committee agreed that the current scheduling of tributyltin oxide remained appropriate.

The Committee further agreed to defer the scheduling of triclosan until the outcome of the NICNAS PEC review was completed and received.

6.12 N-TALLOW-1,3-PROPANEDIAMINE DIACETATE & TALLOW ALKYLAMINE ACETATES

PURPOSE

The Committee considered the scheduling of N-tallow alkyl-1,3-propanediamine diacetate and tallow alkylamine acetates.

BACKGROUND

XXXXXXXX applied for the registration of a new product XXXXXXXX which contains two new active constituents, N-tallow alkyl-1,3-propanediamine diacetate XXX g/L and tallow alkylamine acetates XXX g/L. The two active constituents required approval and poison scheduling.

The two active ingredients are fatty nitrogen derived (FND) surfactants. Both are amine salts derived from tallow oil, and are mixtures of saturated hydrocarbons with varying chain length (C_{11}-C_{17}). The mono-acetate derives from a simple primary amine whereas the diacetate is a propylamine extended version of the mono-acetate. Both molecules are water soluble in their acetate salt form, in contrast to their lack of solubility as free amines. They each exhibit surfactant-like properties because they possess a positively charged polar ‘head group’ that binds to a solid surfaces, leaving the long chain hydrophobic tail exposed.

The proposed use of XXXXXXXX in Australia involves treatment of land-based cooling systems utilising seawater for industry, hotels, and power station applications. The active constituents in the product function to control juvenile marine organisms (blue mussel, barnacle, chiton and fanworm) in seawater.

The product is not intended for use on food crops or food-producing animals.

DISCUSSION

The sponsor provided no toxicology data on either of the active constituents or the end-use product. According to the sponsor, the main active constituent N-tallow-1,3-propanediamine diacetate is formed "in situ" during manufacture, and no toxicological studies had been conducted on the chemical by the sponsor.

Two chemically-related alkyl-ethoxylated propoxylated tallow amines, alkoxylated fatty alkylamine polymer (CAS No: 68213-26-3, trade names Armoblen 557 and Armoblen 600) with limited toxicology data, have previously been assessed by TGA. Both substances are polymerisation products of tallow amine with ethylene and propylene oxide. The polymers have low oral toxicity and moderate inhalational toxicity in rats, and are slight irritant in rabbit eyes and skin. The polymers did not display genotoxic action *in vitro*. Alkoxylated fatty alkylamine polymer is currently included in Schedule 6 of the SUSDP, except in preparations containing 50% or less (S5), or in preparations containing 20% of less (exempt).

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

Neither amines, tallow alkyl, acetates or amines, N-tallow alkyltrimethylenedi-, acetates are included in the SUSDP. The Fatty Nitrogen Derived Ether Amines Category of chemicals (fatty amines) are very similar in structure and function, with minimal differences among the alkyl substituents. The large database for the FND categories of chemicals indicates that the structural differences in these large alkyl chains do not appear to result in significant differences in toxicity or mutagenicity.

Based on the toxicological assessment described above, the OCS considered that the Fatty Nitrogen Derived Ether Amines Category of chemicals to be of low oral toxicity, and likely to have low to moderate acute dermal and inhalational toxicity. These chemicals were unlikely to be either mutagens or reproductive/developmental toxins. However, they are likely to be highly irritating and/or corrosive to the eyes, skin and mucosa.

The OCS suggested that the NDPSC may consider it appropriate to include fatty nitrogen derived ether amines as a group (including amines, tallow alkyl, acetates and amines, N-tallow-alkyltrimethylenedi-, acetates) in Schedule 6 of the SUSDP.

DECISION 2005/44 - 21

The Committee, having regard to the likelihood that N-tallow alkyl-1,3-propanediamine diacetate and tallow alkylamine acetates were likely to be highly irritating and/or corrosive to the eyes, skin and mucosa, agreed that they be included in Schedule 6 of the SUSDP.

Schedule 6 – New entry

N-TALLOW ALKYL-1,3-PROPANEDIAMINE DIACETATE and TALLOW ALKYLAMINE ACETATES.

6.13 AQUARIUM CHEMICALS (MALACHITE GREEN, ACRIFLAVINE, METHYLENE BLUE, QUININE, AMINACRINE)

PURPOSE

The Committee considered the scheduling of malachite green, acriflavine, methylene blue, quinine and aminacrine.

BACKGROUND

Ornamental aquarium antiseptic products are a class of products used to aid the control of bacterial and fungal diseases such as finrot, tailrot, white spot and velvet disease in aquarium fish. Their action is one of antisepsis to reduce the number of disease-causing microorganisms in the water and on the fish themselves.

The NDPSC noted that the Australian Pesticides and Veterinary Medicines Authority (APVMA) was considering a number of chemicals for inclusion in a Standard for Listed Registration 1/104: Ornamental Aquarium Antiseptic Products. Products listed under this Standard will not require review by the agencies involved in the National Registration Scheme. The chemicals being considered in this review are acriflavine, aminacrine, malachite green, methylene blue and quinine. These chemicals may be formulated as an aqueous solution of a single active ingredient, or in the following combinations:

(a) malachite green and acriflavine
(b) malachite green, acriflavine and methylene blue
(c) malachite green, acriflavine, methylene blue and phosphoric acid
(d) malachite green, acriflavine, methylene blue and quinine
(e) malachite green, methylene blue and phosphoric acid
(f) malachite green and formaldehyde
(g) malachite green and quinine
(h) acriflavine and methylene blue

The APVMA had proposed that each product be limited to a pack size of 1 litre and with combined active ingredients not to exceed 50 g in total. A maximum concentration had also been set for each of the individual chemicals.

The Committee received advice that a number of similar products have been available on the Australian market for many years and were 'grandfathered' from State regulation lists when the National Registration Scheme commenced in 1991. Table 1 shows the maximum concentration of the substance currently in the marketplace and which would be accepted under the new Standard for Listed Registration.

Table 1.

Chemical	Maximum Concentration in the Product (g/L)
Acriflavine	2
Aminacrine	5
Formaldehyde	37
Malachite green	0.408
Methylene blue	4.08
Phosphoric acid	1530
Quinine	30

Because of OCS concerns about the use of these genotoxic chemicals in products which may be stored and used around the home, the issue of the development of the Standard was referred to the National Drugs and Poisons Schedule Committee (NDPSC).

A copy of the draft Standard and a list of some of the currently available aquarium products was provided to the Committee as an attachment to the OCS Health Assessment Technical Report.

DISCUSSION

Acriflavine

The Committee was advised that there is a paucity of information on acute/short-term effects (oral, dermal, inhalational toxicity, skin and eye irritation, skin sensitisation), developmental toxicity and genotoxicity of acriflavine. Studies showed that acriflavine has moderate toxicity and may be a skin and eye irritant. The genotoxicity studies available indicated that acriflavine is likely to be genotoxic *in vivo*.

It was also recalled that acriflavine has not previously been considered for the purposes of poisons scheduling by the NDPSC.

Based on a rat oral LD_{50} of 64 mg/kg bw, a solution of 2 mg acriflavine/mL would have an estimated acute median lethal dose of 32,000 mg/kg bw. This toxicity is much lower

than the recommended limit of 1,500 mg/kg bw as proposed in the Guidelines for Pesticides used by Householders.

The OCS had suggested that the NDPSC consider placing acriflavine in Schedule 7 of the SUSDP with a cut-off to Schedule 5 for solutions at concentrations of 2.5% or less.

This approach would require labels for ornamental aquarium products submitted under the Standard for Listed Registration 1/104: Ornamental Aquarium Antiseptic Products to have the Schedule 5 signal heading 'Caution'.

It was noted that three acriflavine products (for human use) containing 1mg/mL were listed on the ARTG.

Aminacrine

There is also a paucity of information on acute/short-term effects (oral, dermal, inhalational toxicity, skin and eye irritation, skin sensitisation), developmental toxicity and genotoxicity of aminacrine. Studies showed that aminacrine has moderate toxicity. The genotoxicity studies available indicated that aminacrine is likely to be genotoxic *in vivo*.

Aminacrine when used as a veterinary chemical had not previously been considered for the purposes of poisons scheduling by the NDPSC. Aminacrine is in Appendix B of the SUSDP for human therapeutic use as an antiseptic (and so listed because "the use pattern restricts the hazard") but has not previously been considered toxicologically by the OCS.

Based on a mouse oral LD_{50} of 78 mg/kg bw, a solution of 5 mg aminacrine/mL would have an estimated acute median lethal dose of 15,600 mg/kg bw. This toxicity is much lower than the recommended limit of 1,500 mg/kg bw as proposed in the Guidelines for Pesticides used by Householders.

The OCS had suggested that the NDPSC consider placing aminacrine in Schedule 7 of the SUSDP with a cut-off to Schedule 5 for solutions at concentrations of 2.5% or less.

This approach would require labels for ornamental aquarium products submitted under the Standard for Listed Registration 1/104: Ornamental Aquarium Antiseptic Products to have the Schedule 5 signal heading 'Caution'.

It was noted that two products for human use (Medijel Gel containing 0.5 mg/g aminacrine and Mac-Morrhuol Acridine containing 1mg/kg aminacrine) were listed on the ARTG.

Malachite Green

Information on acute/short-term effects (oral, dermal, inhalational toxicity, skin and eye irritation, skin sensitisation), carcinogenicity, developmental toxicity and genotoxicity of

malachite green is limited. Studies showed that malachite green has moderate acute toxicity.

Malachite green is mutagenic *in vitro* and *in vivo*, and there was equivocal evidence of carcinogenic activity in a female rat study, based on the occurrence of thyroid gland follicular cell adenoma or carcinoma (combined) and marginal increases in hepatocellular adenoma and mammary gland carcinoma.

Malachite green has not previously been considered by the NDPSC for the purpose of poisons scheduling.

Based on a rat oral LD_{50} of 275 mg/kg bw, a solution of 0.408 mg malachite green/mL would have an estimated acute median lethal dose of 674,000 mg/kg bw. This toxicity is much lower than the recommended limit of 1,500 mg/kg bw as proposed in the Guidelines for Pesticides used by Householders.

The OCS had suggested that the NDPSC may wish to consider placing malachite green in Schedule 7 of the SUSDP with a cut-off to Schedule 5 for solutions at concentrations of 10% or less.

This approach would require labels for ornamental aquarium products submitted under the Standard for Listed Registration 1/104: Ornamental Aquarium Antiseptic Products to have the Schedule 5 signal heading ‘Caution’.

It was noted that one product (Skindesign Clarifying Anti Acne Serum) containing 10 micrograms/gram of malachite green was listed on the ARTG.

Methylene Blue

There was a paucity of information on acute/short-term effects (oral, dermal, inhalational toxicity, skin and eye irritation, skin sensitisation), developmental toxicity and genotoxicity of methylene blue. Studies showed that methylene blue has low toxicity but is a severe eye irritant. The genotoxicity studies available indicated that methylene blue is likely to be genotoxic *in vitro*, but it is uncertain whether it is mutagenic or genotoxic *in vivo*. It is also reported to be embryolethal and a developmental toxin.

Methylene blue had not previously been considered as a veterinary active ingredient by the NDPSC.

Based on a rat oral LD_{50} of 1180 mg/kg bw, a solution of 4.08 mg methylene blue/mL would have an estimated acute median lethal dose of 289,000 mg/kg bw. This toxicity is much lower than the recommended limit of 1,500 mg/kg bw as proposed in the Guidelines for Pesticides used by Householders.

The OCS had suggested that the NDPSC consider placing methylene blue in Schedule 7 of the SUSDP with a cut-off to Schedule 5 for solutions at concentrations of 50% or less.

This approach would require labels for ornamental aquarium products submitted under the Standard for Listed Registration 1/104: Ornamental Aquarium Antiseptic Products to have the Schedule 5 signal heading 'Caution'.

It was noted that there were a number of products (for human use) listed on the ARTG where methylene blue was listed as an excipient.

Quinine

Information on acute/short-term effects (oral, dermal, inhalational toxicity, skin and eye irritation, skin sensitisation), developmental toxicity and genotoxicity of quinine is very limited.

Although low level exposure to quinine, used in Indian tonic water as a bittering agent, presents a negligible risk, higher doses are potentially fatal. The lethal dose of quinine for adults is approximately 2 to 8 g or 30 to 120 mg/kg bw. For children this would equate to a total amount of between 300 to 1200 mg. The genotoxicity studies available indicated that quinine is unlikely to be genotoxic *in vivo*.

Quinine for veterinary use had not previously been considered by the NDPSC.

Based on a conservative oral lethal dose of 30 mg/kg bw in adult humans, a solution of 30 mg quinine/mL would have an estimated acute median lethal dose of 1,000 mg/kg bw. This toxicity is higher than the recommended limit of 1,500 mg/kg bw as proposed in the Guidelines for Pesticides used by Householders.

The proposed standard of 30 mg/ml of quinine in aqueous solution could present an unacceptable risk for a listed registered product, as the lethal dose for children would be of the order of 10 to 40 mL. Therefore, the OCS does not recommend that a maximum concentration of 30 mg/mL of quinine in aqueous solution be included in the Standard for Listed Registration 1/104: Ornamental Aquarium Antiseptic Products. The OCS considers preparations of quinine containing less than 10 mg/mL to be acceptable from a toxicological perspective for listable registration.

OCS suggested that the NDPSC consider placing quinine in Schedule 7 of the SUSDP with a cut-off to Schedule 5 for solutions at concentrations of 1% or less.

This approach would require labels for ornamental aquarium products submitted under the Standard for Listed Registration 1/104: Ornamental Aquarium Antiseptic Products to have the Schedule 5 signal heading 'Caution'.

The OCS has also suggested that, for all the substances, the NDPSC may wish to consider other controls eg. Volume limited pack size (current proposed maximum volume is 1 Litre) and the use of child resistant closures.

It was noted that ARTG listed numerous products for human use containing quinine.

Public Comment

The Committee noted public comment in response to the Pre-Meeting Gazette Notice from XXXXXXXX. XXXXXXXX noted that malachite green had a range of other uses including the dyeing of cotton, silk, paper, bamboo, weed, straw and leather. It was also used in the manufacture of paints and printing inks. XXXXXXXX requested that the Committee keep it advised of the outcome.

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The Committee agreed to include acriflavine, aminacrine, malachite green, methylene blue and quinine for veterinary use in Schedule 7 of the SUSDP with appropriate cut-offs to Schedule 5, noting that the limited toxicity data for these substances allowed, with an appropriate cut-off, the inclusion in Schedule 5 of the SUSDP.

Given the nature of the substances, the Committee also agreed that veterinary products containing these substances should be in child resistant containers. As this was a matter for the regulatory authority, viz the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Committee requested that the APVMA be informed of the Committees decision.

Schedule 7 – New entries

ACRIFLAVINE for veterinary use **except** when in Schedule 5.

AMINACRINE for veterinary use **except** when included in Schedule 5.

MALACHITE GREEN for veterinary use **except** when included in Schedule 5.

METHYLENE BLUE for veterinary use **except** when included in Schedules 4 and 5.

QUININE for veterinary use **except** when included in Schedule 5.

Schedule 5 – New entries

ACRIFLAVINE in preparations for veterinary use containing 2.5 per cent or less of acriflavine.

AMINACRINE in preparations for veterinary use containing 2.5 per cent or less of aminacrine.

MALACHITE GREEN in preparations for veterinary use containing 10 per cent or less of malachite green.

METHYLENE BLUE in preparations for veterinary use containing 50 per cent or less of methylene blue.

QUININE in preparations for veterinary use containing 1 per cent or less of quinine.

PHARMACEUTICALS

13. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

13.1 PSEUDOEPHEDRINE

PURPOSE

The Committee considered the scheduling of pseudoephedrine.

BACKGROUND

The June 2002 NDPSC Meeting rescheduled all OTC single-active immediate release pseudoephedrine preparations from Schedule 2 (S2) to S3 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. The Committee also included pseudoephedrine in Appendix H to maintain the status quo on advertising. Since this date, the Committee has maintained a watching brief of the remaining S2 pseudoephedrine preparations.

The October 2004 NDPSC Meeting considered rescheduling the remaining S2 pseudoephedrine preparations to S3. The Committee remained concerned by ongoing reports of what appeared to be an increasing level of diversion of pseudoephedrine products into the illicit drug trade with the increasing detection of clandestine laboratories manufacturing methylamphetamine in a number of States. The Committee was also informed 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. In addition, the Committee considered the draft final report on a research project funded by XXXXXXXX at the request of XXXXXXXX. The report XXXXXXXX was aimed at determining the extractability of pseudoephedrine from various formulations and the ease at which pseudoephedrine could be converted into methylamphetamine. Members noted that the majority of products in the report, which did not appear to include liquid or slow release preparations, provided reasonable to high yields of methylamphetamine and that the approach of selective rescheduling to S3 of high risk products was unlikely to offer a long term solution to the problem. The report also showed that the type of products targeted for diversion after single-active products were rescheduled to S3 in June 2002 had shifted to combination products. The report therefore concluded that to reduce the risk of the diversion of pseudoephedrine containing products to the illicit drug production market, it would be important to consider the full range of products available on the market and ensure that appropriate restrictions were uniformly applied to all product lines.

The October 2004 NDPSC Meeting agreed to take no scheduling action so as 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 and indicated that it was willing to consider rescheduling all pseudoephedrine products to S3 or S4 in the future, if the diversion problem remained unresolved. The Committee also recommended that in the interim, all pharmacy organisations and XXXXXXXX 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 and all jurisdictions should enforce any mandatory requirements for all S2 pseudoephedrine products to be made inaccessible for self-selection by the public. The Committee also requested the TGA to facilitate the registration of new products containing phenylephrine as the decongestant as an alternative to pseudoephedrine.

The February 2005 NDPSC Meeting continued its consideration of the issue of pseudoephedrine diversion to the illicit drug trade and noted the initiatives put in place by various organisations to help address the problem of pseudoephedrine diversion. In particular, members noted the recommendations of the XXXXXXXX that a number of voluntary measures be implemented as an alternative to reclassifying combination pseudoephedrine products to S3. Members also noted the Pharmacy Guild of Australia's *Project Pseudo* which was a set of voluntary guidelines for community pharmacists and their staff in order to assist in dealing with requests for pseudoephedrine based products and to reduce the flow of such products to illegal activities, and the revision of the Australian Self-Medication Industry (ASMI's) *Code of Conduct – Helping Prevent the Diversion of Pseudoephedrine-Containing Non-Prescription Medicines* to incorporate the XXXXXXXX recommendations. While the Committee expressed its full support for the initiatives that have been implemented, members agreed that there was a need to measure their effectiveness in reducing the rate of pseudoephedrine diversion and foreshadowed to consider this specific issue at the June 2005 meeting. The Committee also agreed to reconsider the scheduling of pseudoephedrine at the June meeting where it would consider the possibility of moving all pseudoephedrine products to more restrictive Schedules including those which would require a prescription for supply, the possible removal of pseudoephedrine from Appendix H and the variation to the usual implementation date of any decision.

DISCUSSION

XXXXXXXX, XXXXXXXX and XXXXXXXX participated in the discussion of this item via telephone.

Following the February 2005 NDPSC Meeting, advice from XXXXXXXX was sought regarding XXXXXXXX's view of the place of pseudoephedrine in contemporary medical practice in Australia and the potential implications to legitimate consumers of pseudoephedrine should this substance be reclassified as a prescription medicine. The Committee noted the following response from XXXXXXXX:

- Pseudoephedrine has a place in the treatment of acute rhinitis.

- Should pseudoephedrine be listed as S4, it would place a significant burden upon the public in terms of access to an effective medication for a condition that generally does not require a doctor's visit.
- It would seem appropriate to list all pseudoephedrine medications as S3 and only be provided by a pharmacist.
- The amount of pseudoephedrine supplied in a single package should be reduced to three or four days' supply.

The Committee noted the following pre-meeting submissions:

- At its extraordinary May 2005 meeting, the National Working Group on the Prevention of the Diversion of Precursor Chemicals into Illicit Drug Manufacture (the Working Group) considered all issues relevant to the scheduling of pseudoephedrine, including the implications for diversion of pseudoephedrine into illicit drug manufacture. The Working Group included members from the community pharmacy sector, law enforcement agencies, health regulators, forensic services and the pharmaceutical industry. The Working Group highlighted that the dangers associated with the production and use of methamphetamine are considerable and well documented in Australia and internationally. These harms relate to individual health risks and social harm in using methamphetamine, the risks associated with the manufacture of methamphetamine in clandestine laboratories and the costs borne by the community arising from both the use and production of methamphetamine. As such, the Working Group considered that these harms necessitate a change to scheduling, particularly when the rescheduling of single-entity pseudoephedrine products resulted in an immediate and marked reduction in those preparations being diverted into illicit drug manufacture. The Working Group thus made the following recommendations to the Committee with a view to achieving a substantial reduction in pseudoephedrine diversion from pharmacies into illicit drug manufacture and the harms caused by methamphetamine to the Australian community:
  - That the Committee should list pseudoephedrine in S3 of the SUSDP. There was clear evidence that the community pharmacy sector remained the weakest link in the pseudoephedrine supply chain and therefore this point in the supply chain warranted tighter regulation to reduce the supply of methamphetamine to the community.
  - That, as a means of reducing diversion, the Committee should give consideration to limiting the amount of pseudoephedrine available over the counter to 720mg per pack. Such a restriction would impose an additional and valuable constraint on the activities of pseudo runners.
  - That the Committee should refer the issue of advertising to the Therapeutic Goods Advertising Code Council (TGACC), recommending that any advertising of products containing pseudoephedrine should include an agreed statement advising consumers that they would be required to discuss their purchase and product choice with the pharmacist.

- XXXXXXXX, a consultant psychiatrist and spokesperson for XXXXXXXX, highlighted that psychiatric morbidity associated with methamphetamine use is a significant problem facing health services. XXXXXXXX also indicated that methamphetamine use in humans is associated with significant risks to the brain such as structural brain damage, neurotransmitter abnormalities and psychiatric illness including dependence syndrome and methamphetamine-related psychoses. In a study conducted by Heffernan *et al* (*MJA 2003; 179 (8): 408-411*) of approximately 300 consecutive receptions at the Brisbane City Police Watch House in February and March 2001, about 60% of all females and 45% of all males interviewed had an amphetamine use disorder (either a severe problem with abuse or dependence). In both genders, the prevalence of amphetamine use disorders was higher than for any other licit or illicit substance and that nearly all of these individuals had significant psychiatric morbidity indicating the need for further psychiatric assessment and management. As such, XXXXXXXX was of the view that methamphetamine posed a serious public health problem and the consequences for the individual, the community and health services were likely to progress given that there seemed little indication of any difficulty in obtaining supply of the substance.
- XXXXXXXX and XXXXXXXX recommended that the maximum quantity available for any preparation in S3 should be 720 mg regardless of dose form and that pseudoephedrine be removed from Appendix H. Although the Victorian Board supported the proposal that all preparations containing pseudoephedrine, except when included in S4, be included in S3, XXXXXXXX expressed its concern about the potential impact of rescheduling all existing S2 pseudoephedrine products to S3 which would create additional interruptions and distractions to the dispensing role of the pharmacist and thus, increase the risk of dispensing errors.
- XXXXXXXX commented that all existing S2 pseudoephedrine preparations would be appropriately placed in S3 where pharmacist intervention would aid in the reduction of the problem of illicit diversion. XXXXXXXX was also in agreement with the removal of pseudoephedrine from Appendix H.
- XXXXXXXX was firmly opposed to the option of rescheduling pseudoephedrine to higher Schedules requiring a prescription as the safety profile of pseudoephedrine did not warrant prescription only access and the potential increase in Medicare and related costs through increased medical consultations cannot be justified. The recent position of XXXXXXXX on the scheduling of pseudoephedrine is that pseudoephedrine products should be scheduled no higher than S3 with a maximum pack size of 600 mg of pseudoephedrine per pack and that advertising to the public of such products should be prohibited.
- Although XXXXXXXX recommended that an appropriate Schedule for pseudoephedrine was S3, it expressed its concerns about any scheduling changes to the existing S2 pseudoephedrine products. XXXXXXXX highlighted the following concerns:
  - There was a lack of uniformity in professional and regulatory controls between states and territories.

- There appeared to be a lack of national data on patterns of diversion to (i) determine the impact of regulatory and professional control measures, and (ii) to assess the need for modifications to control measures that would impact on a particular part of the pseudoephedrine and precursor chemicals supply chains.
- Since XXXXXXXX launch of *Project Pseudo* in March 2005, there was a 10% overall decrease in sales of pseudoephedrine solid dose pack to consumers, with a 15% reduction for 'high risk' > 30 mg pseudoephedrine/dose and a 5% reduction for 'low risk' < 30 mg pseudoephedrine/dose. Although the figures were encouraging, XXXXXXXX acknowledged that there was limited time for *Project Pseudo* to have an impact.
- Any additional legal requirements imposed on pharmacists at a time of workforce shortage could adversely impact on other health services provided by the pharmacist. This would remove time from services such as counselling and provision of prescription medicine, and greater disruptions to workflow which would create the potential for increased dispensing errors.

- XXXXXXXX strongly urged the Committee to take into account the positive outcomes of ongoing activities that have been implemented to curb the illicit diversion of pseudoephedrine. XXXXXXXX claimed that recent data indicated that there was a reduction of sales of pseudoephedrine products. In the first quarter of 2005 compared to the same period in 2004, there was a 28% decline in sales of such products into pharmacies and a 15% decline of sales from pharmacies to consumers. Company sales into wholesalers were also reduced by 15 to 50% over the last two months, which corresponded to the prime purchasing time for the winter stock-in of cough and cold products. Given that sales have declined across all three parts of the distribution chain, this supported the view that the current measures were beginning to impact on the supply of pseudoephedrine products. XXXXXXXX considered, however, that these measures needed to be given more time to take a more widespread effect. In light of these recent sales data, XXXXXXXX recommended the following:
  - All solid dose combination products, which include the high risk antihistamine combinations, containing more than 720 mg but less than 1800 mg per pack of pseudoephedrine be rescheduled to S3.
  - All solid dose combination products containing 720 mg or less of pseudoephedrine remain as S2 and should be stored out of reach as per the current voluntary measures.
  - All liquid formulations containing no more than 1000 mg of pseudoephedrine remain as S2 and should be stored out of reach.
  - Pseudoephedrine should remain in Appendix H as there is no proven link between advertising and the illicit diversion.
- Pre-meeting submissions from XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX all opposed to the

rescheduling of all pseudoephedrine products and the removal of pseudoephedrine from Appendix H. Moreover, XXXXXXXX objected to the rescheduling of its liquid products, XXXXXXXX and XXXXXXXX, as there was no evidence that pseudoephedrine could be extracted from liquid formulations which the Committee had previously noted from the XXXXXXXX report at the October 2004 meeting. XXXXXXXX also pointed out that sales figures of these liquid products showed a decline in sales.

- XXXXXXXX commented that any decision to impose a limit on the packaging for pseudoephedrine would need to take into account the average duration of illness which the products are indicated for and the appropriate duration of treatment. The sponsor proposed a limit of 900 mg of pseudoephedrine per pack.
- XXXXXXXX remarked that the rescheduling of pseudoephedrine should be limited to products with clear evidence of being targeted for diversion and that timing of implementation of any rescheduling should take into account the size of the category and extent of change required, for example changes to the packaging, PI & CMI documents. Advertising of pseudoephedrine products should be permitted to continue. XXXXXXXX further highlighted that the recommendations of the October 2004 NDPSC Meeting had been complied with and that there should be sufficient time to ensure the effectiveness of the recommendations.
- A late submission from XXXXXXXX supported the uniform S3 scheduling of all pseudoephedrine products and the removal of pseudoephedrine from Appendix H.
- XXXXXXXX expressed a concern that the widespread problem on the illicit diversion of pseudoephedrine has penalised legitimate consumers due to less accessibility of such products. XXXXXXXX proposed that appropriate consumer engagement and participation in this decision-making were essential.

The Committee also acknowledged the following recommendations from the draft minutes of the June 2005 XXXXXXXX Meeting:

- XXXXXXXX supported the inclusion in S3 of all pseudoephedrine preparations except those currently included in S4 and the removal of pseudoephedrine from Appendix H.
- The inclusion of pseudoephedrine products in S3 would not disadvantage legitimate consumers as replacement products containing phenylephrine would be available as S2.
- The S3 entry for pseudoephedrine should limit supply to packs containing a maximum quantity of pseudoephedrine consistent with the New Zealand limit for classification as a ‘Controlled Drug C3’, ie. 1.8 g.
- XXXXXXXX did not consider it necessary to reschedule all pseudoephedrine products to S4.

The Committee noted that, although the available sales data for the first three months of 2005 showed an apparent reduction in sales of pseudoephedrine products, the percentage

of products that were being diverted was not known. A member added that the probable reasons for this reduction are that pharmacies and wholesalers were not purchasing large stocks due to the uncertainty of the future scheduling of pseudoephedrine by the NDPSC, and that pharmacies have deferred their normal early autumn "winter buys" due to protocols requiring pharmacies not to buy in large quantities of pseudoephedrine products at one time."

The Committee was also provided a paper XXXXXXXX by XXXXXXXX. The paper, which reviewed the findings from MRI/MRA (magnetic resonance imaging/magnetic resonance angiography) of patients with cerebral complications from illicit drug use in XXXXXXXX over the last 12 months, concluded that given the ready availability of illicit amphetamines in the community, emergency departments are increasingly confronted with patients suffering cerebral side-effects from methamphetamine use.

A member advised that the XXXXXXXX, at its May 2005 meeting, agreed that all existing pseudoephedrine products in S2 be rescheduled to S3 and that only sales of those combination products containing an antihistamine and pseudoephedrine were to be recorded.

Another member informed that the Working Group had previously discussed liquid preparations of pseudoephedrine and that it had agreed that the diversion of liquid pseudoephedrine products into illicit drug manufacture was also a problem. In addition, there were reports from XXXXXXXX police of pseudoephedrine liquid products being targeted for illicit use. Furthermore, members recalled that the February 2005 NDPSC Meeting noted a XXXXXXXX report on pharmaceutical preparations as a source of pseudoephedrine. The XXXXXXXX report, which indicated that there were around 50 products available in New Zealand from which pseudoephedrine could be extracted, also included liquid preparations.

On the basis of all the available information and including the potential harms associated with methamphetamine use, members supported the rescheduling of all pseudoephedrine products, including liquid preparations, to S4 with an S3 cut-off for those preparations containing up to 800 mg or less of pseudoephedrine hydrochloride (or its equivalent) for liquid preparations and 720 mg or less of pseudoephedrine hydrochloride (or its equivalent) for all other dosage forms. It was anticipated that this approach would allow for appropriate restrictions to be uniformly applied to the full range of pseudoephedrine products. It would also remove the problem of a shift in products targeted for diversion since no pseudoephedrine preparations would remain in S2. Furthermore, by limiting the amount of pseudoephedrine per pack in S3, members considered that the resulting maximum pack size was considered sufficient for the treatment of a range of sinus, cold, flu and allergy conditions consistent with the recommended doses for once occurrence of the condition, ie. about three days' supply. Members also agreed that the 800 mg pseudoephedrine hydrochloride limit for liquid preparations should avoid repackaging of existing products with a total volume of 200 mL to 180 mL. The 800 mg pseudoephedrine hydrochloride (or its equivalent) per pack limit for liquid preparations

would allow a maximum concentration of 4 mg per mL of pseudoephedrine hydrochloride in pack sizes of up to 200 mL.

Members noted that there were approximately 290 pseudoephedrine products registered in the Australian Register of Therapeutic Goods (ARTG) for supply in Australia. Of these, it was estimated that about 30 products would be rescheduled from S3 to S4 and about 75 products from S2 to S4. The remaining products which met the proposed pseudoephedrine limit per pack would be rescheduled from S2 to S3.

Members also expressed that in making the rescheduling decision for pseudoephedrine, they were cognisant of the variation between the jurisdiction's interpretations of the SUSDP storage requirements for S3 products. This matter was discussed in detail at item 1.7.1.4.

The Committee also discussed the Appendix H listing of pseudoephedrine. Members were reminded that historically, the inclusion of a substance in Appendix H was generally to inform the public of the S3 availability of a product previously on prescription only and through which advertising of the product may have a potential public health benefit. However, to permit advertising to the public of a substance which has been rescheduled from S2 to S3 to reduce harm, albeit in this instance from diversion to manufacture an illicit substance, was considered as not being appropriate from a public health perspective. In addition, members accepted that pseudo-runners generally would have specific information on the product that they intend to purchase and were unlikely to be influenced by advertising. Furthermore, a member informed that data from the *2004 Non-Prescription Medicine Purchasing Behaviour Study* conducted in 15 pharmacies in XXXXXXXX and XXXXXXXX indicated that branded advertising did not have any effect on the purchasing behaviour of pseudoephedrine products. Since the Committee was not in favour of the continued listing of pseudoephedrine in Appendix H on the basis of public health concerns, it would not be relevant to refer the issue of advertising to the TGACC as recommended by the Working Group.

The Committee considered whether it would be appropriate to bring forward the implementation date for the rescheduling of pseudoephedrine. After a full discussion and taking into account the task of communication and marketing changes that would be involved, the Committee agreed that the standard effective date of 1 January 2006 would be appropriate.

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On the basis of the available information and in the interest of public health and safety, the Committee agreed to reschedule all pseudoephedrine products to S4, with a cut-off to S3 for liquid preparations containing 800 mg pseudoephedrine hydrochloride (or its equivalent) or less per pack or for other preparations containing 720 mg pseudoephedrine hydrochloride (or its equivalent) or less per pack. The decision was based on the following:

- Pseudoephedrine is the essential precursor for methamphetamine production.
- The harms associated with the production and use of methamphetamine are considerable.
- Rescheduling all pseudoephedrine preparations to S4 with the S3 cut-off limits should reduce the amount of pseudoephedrine diverted from pharmacies into illicit methamphetamine manufacture and therefore the supply of methamphetamine to the community, while retaining accessibility to genuine consumers of an effective medicine.

The Committee also agreed to remove pseudoephedrine from Appendix H of the SUSDP. Members considered that the continued advertising of pseudoephedrine products was not appropriate given that pseudoephedrine has been rescheduled from S2 to S3 because of public health concerns with diversion.

Schedule 2– Amendment

PSEUDOEPHEDRINE – delete entry.

Schedule 3 – Amendment

PSEUDOEPHEDRINE – amend entry to read:

PSEUDOEPHEDRINE (other than preparations for stimulant, appetite suppression or weight-control purposes) in a primary pack:

(a) containing 800 mg or less of pseudoephedrine hydrochloride (or its equivalent) in liquid preparations; or

(b) containing 720 mg or less of pseudoephedrine hydrochloride (or its equivalent) in other preparations.

Schedule 4 – Amendment

PSEUDOEPHEDRINE – amend entry to read:

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

Appendix H – Amendment

Pseudoephedrine – delete entry.

13.2 COMPOUNDED CODEINE IN XXXXXXXX

PURPOSE

The Committee considered the issue of codeine abuse from XXXXXXXX bilayer tablets.

BACKGROUND

The February 2005 NDPSC Meeting noted a public submission from XXXXXXXX. XXXXXXXX informed that based on the addicts (over 500) that had visited the website, the most abused over-the-counter (OTC) codeine preparation in Australia was XXXXXXXX as separating the codeine from ibuprofen involved simple physical separation of the layers. XXXXXXXX also informed that for those addicts who did not separate codeine, they took large daily doses of ibuprofen and codeine of up to 100 tablets per day. XXXXXXXX requested the Committee to comment on this issue and consider rescheduling XXXXXXXX to Pharmacist-Only Medicine as was the case for XXXXXXXX to reduce the rate of addiction. The Committee agreed that this may be a formulation issue for consideration at the June 2005 meeting.

Further to XXXXXXXX's letter to the NDPSC, XXXXXXXX also wrote to the TGA's OTC Medicine Section seeking to have the formulation of XXXXXXXX amended so that the ibuprofen and codeine were equally distributed within the tablet. The OTC Medicines Section had advised XXXXXXXX to contact the sponsor which XXXXXXXX had done several times by e-mail. To date, XXXXXXXX has not received a response from the sponsor.

Following the February 2005 NDPSC Meeting, comment was sought from XXXXXXXX concerning the formulation issue with XXXXXXXX.

XXXXXXXX tablets are currently listed as Schedule 2 (S2) in packs of XXXs and XXXs, while packs of XXXs are classified as S3.

DISCUSSION

The Committee was informed that there were XXXXXXXX products registered in the ARTG:

[4 Paragraphs deleted].

The Committee also discussed the appropriateness of the scheduling of bilayer/multilayer formulations. It was noted that the SUSDP in Part 1, Interpretation defined 'compounded' as, in relation to a substance, "combined with one or more other therapeutically active substances in such a way that it cannot be separated from them by simple dissolution or other simple physical means." In addition, members recalled that the October 2002 NDPSC Meeting held the view that combination products including bilayer preparations where a substance could be readily separated or extracted from other components in the formulation by simple dissolution or other physical means were not included in the definition for 'compounded' in the SUSDP. Members also noted the definition of 'multilayer tablet' in the TGA's Australian approved terminology for medicines *viz,* "a compressed tablet comprising two or more layers of different composition and that the layers may be concentric (compressed coated) or parallel."

Given the SUSDP interpretation of 'compounded' and that the S2, S3 and S4 codeine entries relate only to compounded preparations, members agreed that the current S2 scheduling of XXXXXXXX bilayer tablets appeared to be incorrect and that the accurate scheduling for this product should be S8. Members agreed that the sponsor and the OTC Medicines Section should be advised of this scheduling interpretation.

The Committee also agreed to consider the possibility of amending the SUSDP interpretation of 'compounded' to add a statement to the effect that 'compounded' does not include bilayer/multilayer preparations at the next meeting.

OUTCOME

[Paragraph deleted].

The Committee also agreed that XXXXXXXX and the OTC Medicines Section should be advised that while the bilayer formulation of XXXXXXXX remained in the ARTG, the correct scheduling for this product is S8.

In addition, the Committee agreed to foreshadow the consideration of the possible amendment to the SUSDP interpretation of 'compounded' at the October 2005 meeting to add a statement to the effect that 'compounded' does not include bilayer/multilayer preparations.

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

14.1 SUSDP, PART 4

14.1.2 SUMATRIPTAN

PURPOSE

The Committee considered the scheduling of sumatriptan.

BACKGROUND

Sumatriptan is a selective serotonin agonist that acts at 5-hydroxytryptamine$_{1B/1D}$ receptor subtype (5-HT$_{1B/1D}$) receptors. Activation of 5-HT$_{1B}$ receptors produces vasoconstriction of cranial arteries while activation of 5-HT$_{1D}$ receptors on nociceptive trigeminal nerve afferents reduces the release of vasoactive neuropeptides and inhibits transmission via second-order neurons of the trigeminocervical complex. These actions correlate with relief of migraine headache.

Sumatriptan was first considered by the Committee at the August 1992 meeting, when it was included in Schedule 4 (S4) following the recommendation of approval by the 157th

ADEC meeting to register XXXXXXXX tablets containing sumatriptan for the acute relief of migraine. XXXXXXXX tablets were first marketed in Australia in 1992.

Sumatriptan and the other 5-HT_1 agonists such as naratriptan and zolmitriptan are available as Prescription Only Medicines.

DISCUSSION

XXXXXXXX submitted an application to include oral preparations of sumatriptan XXX mg in packs of XXX tablets (XXXXXXXX) for the treatment of migraine attacks in S3 and Appendix H of the SUSDP. The Committee noted the following points which the applicant highlighted in support of the proposal:

- There is a clear, unmet consumer need for more effective OTC migraine treatment.
- The last 10 years experience with sumatriptan tablets revealed a favourable adverse event profile.
- Migraine is widely recognised as a self-limiting, self-recognisable condition.
- OTC availability of XXXXXXXX with the support of pharmacist intervention would promote optimal early treatment when migraine headache begins, faster relief and optimal treatment outcome.
- XXXXXXXX is to be used for the treatment of acute migraine attacks. The proposed dosage is one 50 mg tablet to be taken as soon as possible after the onset of a migraine headache. If there is a response to the first tablet but the symptoms recur, a second dose may be taken at least 2 hours after the first dose. If there is no response to the first dose, a second dose should not be taken.
- Sumatriptan has a low abuse potential. There are few reports of overdose or abuse and little evidence of drug-induced daily headache with sumatriptan.
- The possibility of childhood poisoning is reduced because the proposed pack size is limited to XXX XXX mg tablets and packaged in aluminium foil blister contained in cardboard carton. Single oral doses of up to 400 mg in adults have not been associated with significant adverse effects.
- Sumatriptan is rapidly eliminated from the systemic circulation and has a high clearance and short elimination half life. The major metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine and has no known 5-HT_1 or 5-HT_2 activity. Thus, doses for single migraine attacks up to 3 times per month would not lead to bioaccumulation.
- A working draft of the Migraine Questionnaire check-list is currently being developed in the UK and Australia to assist the pharmacist in assessing the suitability of XXXXXXXX for a consumer following review of the consumer's medical history including migraine symptoms, use of concomitant medication and assessment of

cardiac risk. In addition, an educational program for pharmacists is being developed to facilitate appropriate recommendation for XXXXXXXX.

- Inclusion of sumatriptan in Appendix H would educate and heighten awareness of an effective OTC migraine treatment that is available from pharmacists, improve quality of life, reduce absenteeism and avoid inappropriate drug use patterns due to the unmet consumer need for more effective OTC migraine treatments. In addition, XXXXXXXX undertakes to conform to all the conditions and provisions as specified in the *Therapeutic Goods Advertising Code* (TGAC).

Following assessment of the sponsor's application, the Committee noted the following points from the NDPSC evaluation report:

- An overview of the efficacy trial dataset provided in the submission clearly demonstrated the efficacy of sumatriptan in its anti-migraine properties.
- Safety data from the clinical trial dataset suggested that sumatriptan XXX mg was generally well tolerated both as a single dose and when used as a repeat dose for headache recurrence. Most studies indicated a dose response, with a higher incidence of adverse events (AEs) for sumatriptan 100 mg compared to 50mg.
- The submission provided a safety overview from the sponsor's worldwide safety database on spontaneous AEs, the Australian Drug Reactions Advisory Committee's (ADRAC) database and published literature which revealed the following:
  - Common AEs (>1/10) were listed as tingling, dizziness, drowsiness, transient increase in blood pressure, flushing, nausea and vomiting, sensations of heaviness, pains, sensations of heat, pressure or tightness, feelings of weakness and fatigue. Less common events (<1/1,000) included hypersensitivity ranging from skin reactions to rare cases of anaphylaxis, seizures, nystagmus, scotoma, flickering, diplopia, reduced vision, loss of vision (usually transient), bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction, hypotension, Raynaud's phenomenon, ischaemic colitis and abnormalities in liver function tests.
  - As of 31st March 2004, the spontaneous post-marketing AE reports received for all formulations of sumatriptan, with 30% involving the tablet formulation, showed that although cardiovascular and neurological events were uncommon, if present, they typically occurred as serious and potentially fatal. 20% of serious cases were cardiac disorders such as myocardial infarction, angina and coronary artery spasm. Palpitations and tachycardia were also frequently reported. 27% of serious cases of nervous system disorders included cerebrovascular accidents, cerebral infarction, cerebrovascular spasm, ischaemic stroke, transient ischaemic attacks, hemiparesis, hemiplegia, paralysis, spastic paralysis and aphasia.
  - Reports from the ADRAC database up to 28th January 2005 referred to 628 AE reports in which sumatriptan was a suspect drug. Commonly reported events (>50 occasions) were nausea, ineffectiveness, dizziness, paraesthesia and chest pain. 54% of the reports related to oral administration, 23% to subcutaneous

injection and 18% were of unknown route of administration. There were three cases (0.5%) in which the outcome was fatal.

– A total of 531 reports of hypertension were identified in the sponsor's safety database to December 2002 and other AEs were also reported in association with hypertension such as chest tightness, palpitations, tachycardia, bradycardia, arrhythmias, convulsions, cerebrovascular accidents and allergic reactions. 24% of these reports involved the tablet formulations. The sponsor's database to 31 March 2004 showed that, of the 641 reports suggestive of myocardial ischaemia, approximately two thirds were serious. About a third of the reports documented one or more risk factors, excluding age, for myocardial ischaemia most commonly smoking, hypertension, hypercholesterolaemia or diabetes.

- Whilst sumatriptan is used for a common, easily recognisable condition, significant caveats with regard to its use in the setting of patients on other drugs, history of cardiovascular or cerebrovascular disease and rare but not uncommonly serious and/or fatal cardiac events mandate its use in the setting of medically supervised initiation and monitoring of therapy. Thus, it is recommended that sumatriptan remain in S4.
- Because the S3 request is not supported, listing in Appendix H is not relevant.

The Committee acknowledged the following pre-meeting comments in support of the rescheduling of sumatriptan to S3:

- Although XXXXXXXX considered that S3 availability of sumatriptan may be of benefit to consumers, XXXXXXXX highlighted that the Committee may require additional consideration since sumatriptan is under authority restriction in the PBS. XXXXXXXX also emphasised the need for sponsors to work together with XXXXXXXX and adequate time to develop and disseminate the necessary resources for the pharmacy profession. However, XXXXXXXX was opposed to Appendix H listing until such time as the impact of any scheduling change could be assessed.
- XXXXXXXX and XXXXXXXX supported the S3 proposal for sumatriptan 50 mg but opposed its inclusion in Appendix H as they were of the view that it would be inappropriate to create a public demand for a product that is contraindicated in a number of circumstances. In addition, XXXXXXXX commented that such advertising would undermine the pharmacist's role in the decision to, or not to, supply the product and be contrary to the principles of quality use of medicines for S3 medicines. XXXXXXXX suggested that this item be deferred to the next NDPSC meeting to allow the pharmacy profession to design educational material and a set of protocols for supply.
- XXXXXXXX expressed its view that provided that appropriate measures for diagnosis are in place, the availability of sumatriptan should not be limited.

The Committee acknowledged the following pre-meeting comments that were against the rescheduling of sumatriptan to S3:

- XXXXXXXX, XXXXXXXX and XXXXXXXX considered that sumatriptan 50 mg should remain as S4 due to the following concerns:
  - Rescheduling sumatriptan to S3 would be inconsistent with the policies for quality use of medicine.
  - Sumatriptan is specifically indicated for the acute treatment of migraine headaches and cluster headaches which both require medical diagnosis.
  - Consumers with non-specific headache might use sumatriptan if it is available without a prescription. On the other hand, consumers with migraine or cluster headache might use more than the dose recommended in any 24 hour period and/or use it on a regular basis rather than seek appropriate prophylactic therapy. This has the potential to be particularly hazardous given the vasospastic action of sumatriptan.
  - The contraindications and side effects associated with sumatriptan strongly indicate its continued listing as S4.
  - The Schedule of Pharmaceutical Benefits (PBS) lists sumatriptan as an authority required prescription with the following caution and restrictions:

CAUTION:

Sumatriptan is contraindicated in patients with known or suspected coronary artery disease. The drug should not be used within 24 hours of ergotamine or dihydroergotamine use.

Authority required

Migraine attacks in patients receiving, or who have failed a reasonable trial of, prophylactic medication and where attacks in the past have usually failed to respond to oral therapy with ergotamine and other appropriate agents, or in whom these agents are contraindicated.

NOTE:

No applications for increased maximum quantities and/or repeats will be authorised.

  - Given the current PBS authority restriction on sumatriptan, one respondent was of the view that it would be unreasonable to reschedule it to S3.

- Furthermore, XXXXXXXX believed that quality use of medicines was best served by an accurate differential diagnosis and the application of a treatment protocol. In addition, XXXXXXXX considered that the development of a professional protocol and education of community pharmacy staff was essential to ensure that the OTC management of migraine therapy with sumatriptan was well understood and that the protocol was routinely applied. However, as no such protocol has been developed, XXXXXXXX was not prepared to support sumatriptan in S3.

The Committee discussed the diagnosis of migraine. Members agreed that migraine was a condition that required a thorough clinical diagnosis to exclude other causes of

headache or the presence of an underlying specific organic cause. A member, however, informed that a recent review article on migraine (*Int J Pharm Med 2004;18:325-335*) indicated that physicians diagnose migraine correctly only in about 50% of presenting patients with migraine.

The Committee also expressed concerns on the sponsor's draft *Migraine Questionnaire* which was in the form of a checklist to be completed jointly by the pharmacist and consumer to assist the pharmacist in the accurate diagnosis of migraine. The sponsor had indicated that the questionnaire was still in the process of being developed and modified to the requirements of Australian pharmacists. Members were therefore concerned that there was no evidence of a suitable validated questionnaire for the diagnostic screening test for migraine by pharmacists which was distinct from educational materials.

The Committee also discussed the safety profile of sumatriptan. A member informed that from the submitted data, the sponsor's database indicated that about a third of the reports of cardiovascular events documented one or more risk factors (excluding age) for myocardial ischaemia, most commonly smoking, hypertension, hypercholesterolaemia or diabetes. Another member highlighted that the submission stated that retrospective surveys in clinical practice suggested that the incidence of some form of chest symptoms affected approximately 20% of patients treated with oral sumatriptan and up to 41% of those treated with subcutaneous sumatriptan. As such, members were concerned that pharmacists were not equipped at this stage to deal with side effects such as chest symptoms in the pharmacy setting. Given the contraindications and serious and potentially fatal cardiovascular and cerebrovascular side effects of sumatriptan and that there is a high prevalence of cardiovascular disease (both diagnosed and undiagnosed) in the community, members agreed that the safety profile of sumatriptan required its use in the setting of medically supervised initiation and monitoring of therapy.

A member expressed that, should an individual require an urgent supply of medicines for the treatment of migraine that had been initially diagnosed by a medical practitioner, there was a provision in the SUSDP under Part 1, paragraph 39 which allowed pharmacists to dispense an S4 medicine without a prescription provided that the individual was under medical treatment with the medicine and continuation of medicine was essential, the quantity supplied should not exceed three days medication and that the pharmacist was satisfied that an emergency existed.

OUTCOME

The Committee agreed that the scheduling of sumatriptan in Schedule 4 remained appropriate at this time on the following grounds:

- Migraine is a condition that requires clinical diagnosis. In addition, there was no evidence of a suitable, validated diagnostic tool for pharmacists to accurately diagnose migraine.

- The safety profile of sumatriptan, particularly its cardiovascular and cerebrovascular side effects, and the high prevalence of diagnosed and undiagnosed cardiovascular disease in the community, mandate its use in the setting of medically supervised initiation and monitoring of therapy.

14.1.3 REQUIRED ADVISORY STATEMENTS FOR MEDICINE LABELS

PURPOSE

The Committee considered the foreshadowed decision on the proposed consequential amendments to the SUSDP for consistency with the *Required Advisory Statements for Medicine Labels* (RASML) document.

BACKGROUND

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

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

DISCUSSION

The Committee noted the following pre-meeting submissions:

- XXXXXXXX supported the foreshadowed amendments to the SUSDP for consistency with the RASML.
- XXXXXXXX recommended that the RASML should be brought in line with the SUSDP and not vice versa since any inconsistencies between RASML and the SUSDP would be errors from transcribing, not scheduling.

- XXXXXXXX was opposed to the proposal to amend the SUSDP for consistency with the RASML. In particular, XXXXXXXX was concerned with the entries in the RASML document for eucalyptus oil, marjoram oil, melaleuca oil (tea tree oil) and vitamin A. XXXXXXXX was of the view that the RASML entries for these substances were inconsistent with the SUSDP. [As both XXXXXXXX and XXXXXXXX objected to the current wording in the RASML document and not the foreshadowed amendments to the SUSDP, the Committee agreed that their comments should be brought to the attention of the OTC Medicines Section.]
- XXXXXXXX was unable to provide comment on this item but reserved the right to comment after the June 2005 meeting.
- The OTC Medicines Section supported the foreshadowed amendments with one exception. The OTC Section had initially proposed the following wording to be used in the relevant reverse scheduling entries in the SUSDP:

  "the label on the goods complies with the requirements of the Required Advisory Statements for Medicine Labels"

  However, this statement had been amended for consistency with existing entries in the SUSDP and foreshadowed by the NDPSC Secretariat to read:

  "the label on the primary pack complies with the requirements of the Required Advisory Statements for Medicine Label"

  The OTC Medicines Section thus highlighted that the foreshadowed entries with the amendment of the word 'goods' to 'primary pack' could potentially be interpreted incorrectly. For example, many medicines to which these changes would apply would be supplied in an immediate container but without a primary pack, as currently defined in the SUSDP. Furthermore, since 'container' was not defined in the SUSDP, it could be argued that information included on a primary pack would not constitute a label.

  The OTC Medicines informed that the RASML document currently adopts the definition of 'primary pack' from the *Therapeutic Goods Act 1989* (the Act) and the definition of 'label' from the TGO 69 *viz*:

  ***"Primary pack"**, in relation to therapeutic goods, means the complete pack in which the goods, or the goods and their container, are to be supplied to consumers.*

  ***"Label"** means a display of printed information upon, or securely affixed to, the container and any primary pack containing the goods.*

  To avoid the potential incorrect interpretation and for consistency with the definitions included in the Act and TGO 69, the OTC Medicines Section suggested that the SUSDP interpretation of 'primary pack' and 'label' be amended as follows:

  ***"Primary pack"** means the pack in which a poison, or a poison and its immediate container or immediate wrapper or measure pack are presented for sale or supply.*

  ***"Label"** means a statement in writing on, or securely affixed to, an immediate container and any primary pack of a poison.*

The Committee discussed the issues relating to the definitions of 'primary pack' and 'label'. Members noted that the word 'goods' as initially proposed by the OTC Medicines Section at the February 2005 NDPSC Meeting had been replaced with 'primary pack' for consistency with the wording used throughout the SUSDP given that there is no SUSDP interpretation for 'goods'. Members also noted the following interpretation in the SUSDP:

"Primary pack" *means the pack in which a poison and its immediate container or immediate wrapper or measure pack are presented for sale or supply.*

"Immediate container" *includes all forms of containers in which a poison is directly packed but does not include any such container intended for consumption or any immediate wrapper.*

"Label" *means a statement in writing on a container of a poison.*

Given that the labelling requirements in the SUSDP would continue to apply to products that are not therapeutic goods, members expressed a concern that amending the SUSDP interpretation for 'primary pack' and 'label' as proposed may potentially impact on products that are not therapeutic goods. This may create a loophole for non-therapeutic goods and have the potential effect of undermining the Committee's decisions in relation to exempting products that are not therapeutic goods, such as some essential oils, from the Schedules based on the inclusion of particular warning statements on the label. Additionally, members held the view that the SUSDP should not be brought in line with the RASML but vice versa.

A member suggested that one option was to have two interpretations for 'primary pack' and 'label' in the SUSDP, one for therapeutic goods and the other for non-therapeutic products. Members agreed to consider this matter at the October 2005 meeting.

The Committee therefore did not support the proposed amendment of the interpretation of 'primary pack' and 'label' in the SUSDP to be consistent with the RASML due to concerns on the potential impact on products other than therapeutic goods. As such, members did not proceed further with the foreshadowed consequential amendments to the SUSDP for consistency with the RASML document at this time.

OUTCOME

The Committee did not proceed with the foreshadowed amendments to the SUSDP for consistency with the RASML document at this time. The Committee agreed to reconsider this matter at the October 2005 meeting. Members held the view that the matter on the SUSDP interpretations of 'primary pack' and 'labels' should be resolved before proceeding with the foreshadowed scheduling amendments to the SUSDP. This approach should facilitate the implementation of all the amendments as one package.

14.1.4 PANTOPRAZOLE

PURPOSE

The Committee considered the scheduling of pantoprazole.

BACKGROUND

Pantoprazole is a proton pump inhibitor (PPI) similar to esomeprazole, omeprazole, lansoprazole, and rabeprazole. It is a substituted benzimidazole which accumulates in the acidic compartment of parietal cells after absorption where it is converted to the active form, a cyclic sulfenamide. This then binds to the enzyme hydrogen-potassium-ATP-ase (H+/K+-ATPase) at the secretory surface of gastric parietal cells, blocking the final step of gastric acid production which then leads to inhibition of both basal and stimulated acid secretion. All PPIs are currently listed as Schedule 4 (S4).

Pantoprazole was first considered for scheduling at the February 1995 NDPSC Meeting, when it was included in S4 following the October 1994 ADEC Meeting's recommendation of approval to register XXXXXXXX containing pantoprazole 40 mg for the treatment of duodenal ulcer, gastric ulcer, reflux oesophagitis and gastrointestinal lesions refractory to histamine-2 receptor antagonists (H2RAs). Since January 1994, it has been available in Australia as a Prescription Only Medicine.

The October 1999 ADEC Meeting recommended approval of a new strength of XXXXXXXX containing pantoprazole 20 mg for the acute treatment of reflux oesophagitis and the prevention of relapse of moderate to severe reflux oesophagitis in adults. Furthermore, the April 2001 ADEC Meeting recommended approval to extend the indications for XXXXXXXX 20 mg tablets to include the treatment of heartburn and other symptomatic associated with GORD (symptomatic GORD) and reflux oesophagitis.

DISCUSSION

XXXXXXXX submitted an application to include in S3 oral preparations of pantoprazole 20 mg in primary packs containing 14 or less dosage units for the relief of heartburn and other symptoms associated with GORD. An Appendix H listing was also sought. However, XXXXXXXX had since withdrawn its sponsorship of the application and advised XXXXXXXX as the substitute sponsor. For the purposes of this application, it was proposed that pantoprazole XXX mg as S3 would be referred to as "XXXXXXXX".

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

- It is estimated that between 15 to 20% of adult Australians experience heartburn at least once a week.

- The current choices available in pharmacies for frequent heartburn are antacids which are intended for occasional use and H2RAs for use as required or continually up to 14 days with varying degrees of success. However, antacids are subject to overuse when symptoms are not controlled by this established over-the-counter (OTC) treatment option, while the acid suppressing ability of H2RAs decreases over time.
- The inclusion of pantoprazole 20 mg in S3 would provide a safe and more effective OTC alternative for 14-day treatment of simple cases of frequent heartburn for those whose symptoms are not adequately controlled by antacids and H2RAs.
- PPIs have been shown to be more effective acid suppressants than H2RAs and that intermittent PPI therapy (once daily dosing for 14 days then ceasing treatment until relapse occurs) was successful for patients with mild GORD.
- The proposed indication for S3 pantoprazole 20 mg is the TGA-approved indication for S4 pantoprazole 20 mg *viz*, symptomatic GORD: the treatment of heartburn and other symptoms associated with GORD for adults over 18 years of age. XXXXXXXX is proposed for 14-day treatment of frequent heartburn occurring intermittently. It is not proposed for 'on demand' therapy as this dosage regimen is not appropriate for first time users of Somac Relief.
- The clinical trials data set and the Australian Drug Reactions Advisory Committee's (ADRAC) database for adverse reactions associated with pantoprazole use in Australia supported the safety profile of pantoprazole 20 mg. The nature of adverse events in the clinical trials were generally mild with the most commonly occurring events being headache, diarrhoea, influenza-like symptoms and dizziness which also occurred in placebo-treated patients.
- Pantoprazole has a high therapeutic index, low overdose and abuse potential and low incidence of adverse effects that is likely to require medical intervention. There is neither drug interactions reported with pantoprazole nor with concomitantly administered antacids. Although rare cases of vitamin B12 deficiency have been reported following acid-blocking therapy, this is unlikely to be a risk with the proposed intermittent use of pantoprazole.
- The risk of the use of pantoprazole 20 mg as S3 in masking a serious disease (such as gastric carcinoma and a malignant disease of the oesophagus) and compromising medical management is low and no greater than that with H2RA therapy. This risk is currently managed by pharmacy in the case of H2RAs and in the case of XXXXXXXX, the pharmacist would be assisted by clear labelling instructions of when XXXXXXXX should not be taken and the restricted pack sizes of XXXs and XXXs.
- It is recognised that acid suppression therapy which raises the pH of the stomach contents to > pH4 raises a theoretical risk of increasing the susceptibility to overgrowth of swallowed oral bacterial flora and hence infections. However, this is unlikely to be an issue with the proposed use of XXXXXXXX given that the possible risk is more relevant to long term continuous therapy with acid suppressants.

- Educational programs and materials are under development to assist with the introduction of S3 pantoprazole 20 mg. (Drafts were provided with the submission.)
- Inclusion of pantoprazole in Appendix H would encourage consumers to seek a pharmacist's advice about Somac Relief and their symptoms. Pharmacist screening of consumers could potentially result in a referral to seek medical advice if symptoms do not indicate mild GORD, routine screening for 'alarm symptoms' and thus, health cost saving by earlier identification of consumers with serious underlying illness.

Following assessment of the applicant's submission, the Committee noted the following points from the NDPSC evaluation report:

- The clinical trial dataset, literature and post-marketing reports since pantoprazole was marketed in 1994 revealed a good safety profile.
- The ADRAC database showed that, for the period 2001 to 2004, the total number of spontaneously reported adverse events associated with 20mg oral pantoprazole (n=12) was less than those reported for the 40mg dose (n=227) during the same time period, although the denominators of exposure were not provided.
- From February 1995 to December 2004, there was only one ADRAC bulletin article (*Aust Adv Drug React Bull 2003;22(2):7*) on adverse events related to PPI use. The article stated that while ADRAC had received biopsy-confirmed reports of interstitial nephritis with omeprazole (n=18) and rabeprazole (n=2), there were no reports received for pantoprazole, esomeprazole or lansoprazole.
- Intermittent and on demand therapies with PPIs were recently studied:
  - Bardhan *et al* (*Br Med J 1999;318:502-507*) reported that in a 14-day intermittent dosage regimen of omeprazole or ranitidine, almost half of patients with symptomatic and mild erosive GORD found intermittent treatment successful or acceptable, with 24% of patients switching to daily maintenance therapy. Of those continuing on intermittent therapy, 40% had no further relapse, 30% had one episode, 15% had two episodes and 8% had three episodes during the study follow-up to one year.
  - Three studies by Dettmer *et al*. (*Ailment Pharmacol 1998; 12: 865-872*), Van Zyl (*Eur. J Gastroentrol and Haematol 2000; 12: 197-202*) and Kaspari *et al*. (*Digestion 2001; 63(3)*: abstract) revealed that pantoprazole 20mg once daily versus ranitidine 300mg once daily (or divided) was statistically superior in providing relief of GORD symptoms after 14 days of daily treatment. In these studies, complete relief of key GORD symptoms was achieved in about 65 to 80% in the pantoprazole groups compared with about 50% in the ranitidine groups.
  - A Cochrane review by Pinxteren *et al*. (*Cochrane Database Systematic Reviews; 2004: Issue 3*), which compared the efficacy of short-term PPIs and H2RAs in adults with endoscopic negative GORD, found that when patients were selected based on symptoms, treatment with PPIs was superior to H2RAs in inducing

heartburn remission. Both H2 antagonists and PPIs were well tolerated with comparable profiles of adverse events, close to those of placebo.

- Australian and US practice guidelines (*Gastroenterological Society of Australia 2001. Gastro-oesophageal reflux disease in adults: Guidelines for Clinicians, 3rd Edition* and *DeVault 2005 Updated guidelines for the diagnosis an treatment of gastroesophageal reflux disease*, respectively) suggest that an initial empirical trial with a PPI will provide symptom control and low overall patient cost and is recommended for those with typical symptoms of uncomplicated GORD.
- The PPI omeprazole has been available as OTC in Sweden since April 2000 (omeprazole 10 mg and 20 mg for 14-day treatment of GORD symptoms of heartburn and regurgitation), in the US since June 2003 (omeprazole 20 mg for 14-day treatment of frequent heartburn with a maximum of three courses per year) and in the UK since March 2004 (omeprazole 10mg, maximum 20 mg per day for up to four weeks, for reflux-like symptoms (heartburn)). In addition, the US labelling for OTC omeprazole 20 mg appropriately advises consumers to see their doctor before using this product beyond the recommended 14-day treatment course. This should be required in the Australian submission for pantoprazole.
- Earlier applications for the rescheduling of PPIs to OTC in Australia were rejected largely on the grounds of concern for the ability of the patient/pharmacist to appropriately select a medicine, the suitability of the medicines to be available as OTC and the possibility of the medicine to mask a more serious disease. These issues appeared to have been addressed in the current submission.
- The draft pharmacy education program and materials were noted.
- Based on the efficacy and high potency of pantoprazole when compared to H2RAs for patients with milder forms of GORD symptoms, pantoprazole 20mg per day for short-term use (14 days) should be approved as an S3 medicine as it meets the appropriate criteria for S3 listing, provided that the appropriate warning statements below, as proposed by the sponsor, are included in the Consumer Medicine Information (CMI) and packaging:

> ***Do not use "***XXXXXXXX***" if you:***
> *are allergic to any of the ingredients of* XXXXXXXX
> *are pregnant or breast-feeding*
>
> ***See your doctor immediately if you have:***
> *Trouble or pain on swallowing food.*
> *Vomiting with blood.*
> *Bleeding or black stools*
> *Choking attacks, especially at night.*
> *Unexplained weight loss.*
>
> *These may be signs of a more serious condition.*

Stop taking "XXXXXXXX***" and see your doctor if:***
You are not feeling better or your symptoms worsen.
You need to take XXXXXXXX *for more than 14 days.*
You need to take more than 1 course of treatment every 4 months."

- However, Appendix H listing for pantoprazole was not supported. The criterion for considering advertising as having a potential public health benefit, including more appropriate use of scarce health resources, better informed community and decreased risk of injury due to fewer side effects, are not evident at present for this product. The pattern of OTC use would need to be established with S3 availability.

The Committee acknowledged the following pre-meeting comments:

- XXXXXXXX supported the S3 and Appendix H listing proposal for pantoprazole 20 mg on the condition that all PPIs currently registered in Australia should be considered together as a class given their similar safety and efficacy profiles. Moreover, XXXXXXXX requested that the issues raised against XXXXXXXX previous submission to reschedule lansoprazole be applied during consideration of the pantoprazole submission. XXXXXXXX also contended that the issue of self-diagnosis should not represent a reason against rescheduling the PPIs to S3 since H2RA have already been rescheduled to S2 for the symptomatic treatment of the same clinical condition. In addition, any concern on the use of PPIs in the OTC setting that could result in masking a serious underlying disease could be addressed by ensuring that the OTC pack sizes are restricted for up to two weeks continuous treatment with clear warnings to consult medical advice should the symptoms return after cessation of treatment.
- XXXXXXXX is of the view that it would be appropriate for pantoprazole 20 mg to be classified in S3 but not an Appendix H listing as there is no data or information available in relation to its OTC use in Australia. XXXXXXXX also emphasised the need for the sponsor to work with the PSA to assist with the provision of information and resource materials to all pharmacists.
- XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX were against the proposal. They considered that, although PPIs have a favourable safety profile, PPIs should remain in S4 as a medical diagnosis was required and patients with GORD generally need chronic maintenance therapy and ongoing medical supervision. Due to the greater efficacy of PPIs in relieving symptoms of severe GORD, there may be a greater risk of masking an underlying disease. Current guidelines prepared for pharmacists, such as the National Prescribing Service, do not recommend PPI use for mild intermittent or occasional GORD symptoms but should be managed with lifestyle modification and antacids or H2RAs. Moreover, an Appendix H listing could lead to unnecessary or inappropriate use of pantoprazole 20 mg.

A member pointed out that, in relation to the respondents' concern on the current guidelines prepared for pharmacists, these guidelines, although based on critical analyses of current evidence, also generally reflect the current availability of medicines.

The Committee recalled that the February and June 2003 NDPSC Meetings considered a proposal from XXXXXXXX to reschedule from S4 to S3 oral lansoprazole 30 mg for the relief of symptoms of GORD (heartburn) and acid-related dyspepsia (indigestion) in packs containing not more than 14 days supply and listing in Appendix H. At both meetings, the Committee had agreed that the classification of lansoprazole in S4 remained appropriate mainly on the basis that the data submitted were inadequate to support the proposed use of lansoprazole for intermittent, short-term treatment of the symptoms of heartburn and dyspepsia. In particular, the data contained in the submission focused on the issue of GORD but included little data on the proposed indications (dyspepsia and heartburn). There was neither safety data on the use of lansoprazole for dyspepsia and heartburn nor any evidence to support the statement that PPIs have any advantages over H2RAs in the proposed indication.

However, members concurred that the data submitted for the pantoprazole rescheduling submission adequately addressed the concerns raised by the Committee previously and by pre-meeting respondents who were opposed to the rescheduling of pantoprazole. Additionally, it was highlighted that the proposed S3 indication sought for pantoprazole (heartburn and other symptoms of GORD) was the TGA-approved indication and which the ADEC had recommended approval at its April 2001 meeting.

The Committee's attention was drawn to a statement in the proposed CMI relating to the indication for XXXXXXXX *viz,* "For self-medication of short-term relief and prevention of frequent heartburn associated with gastro-oesophageal reflux." It was pointed out that the TGA-approved indication for pantoprazole 20 mg was for the treatment, not prevention, of heartburn and other symptoms associated with GORD. Members agreed that this should be drawn to the attention of the TGA's OTC Medicines Section.

A member raised a concern regarding the interaction potential of pantoprazole. While noting that the Product Information (PI) for XXXXXXXX stated that there were no clinically significant interactions with a number of drugs including diclofenac, the member highlighted that one literature article (*Drug Metab Dispos 2004;32(8):821-827*) suggested that, in *in vitro* studies, pantoprazole was a competitive inhibitor of both CYP2C9-catalysed diclofenac 4'-hydroxylation and CYP3A4-catalysed midazolam 1'-hydroxylation that were at least two times more potent than omeprazole, esomeprazole, lansoprazole and rabeprazole. The member highlighted that the interaction with diclofenac may be of importance since it was common to prescribe a PPI and a non-steroidal anti-inflammatory drug concurrently. However, members concurred that *in vivo* data was needed to establish the significance of this interaction. Members also agreed that the proposed statements in the CMI "Use XXXXXXXX under medical supervision if you are also taking prescription medicines" and "Tell your pharmacist if you are taking any other medicines…" appeared to adequately address this concern.

Members also discussed a suitable timeframe to implement the rescheduling decision as they considered that a delay in implementation would allow for engagement with the pharmacy profession and the generation and provision of education materials and supply protocols for pharmacists to supply S3 pantoprazole appropriately. Cognisant of the

NCCTG policy that the NDPSC has the discretion to vary the implementation date on a case-by-case basis, members agreed that 1 March 2006 was an appropriate date to implement pantoprazole 20 mg in S3.

DECISION 2005/44 – 24

The Committee agreed to include in Schedule 3 pantoprazole in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of GORD in packs containing not more than 14 days supply. Members were convinced that the available efficacy and safety data supported an acceptable safety profile of pantoprazole 20 mg once daily for 14-day treatment consistent with S3 medicines. It was also agreed that the implementation date for this Decision would be 1 March 2006 to allow adequate time for collaboration with the pharmacy profession and the generation and provision of education materials and supply protocols for pharmacists to supply S3 pantoprazole appropriately.

The Committee also agreed that the warning statements as proposed by the sponsor should be referred to the TGA's OTC Medicines Section for consideration of inclusion into the CMI and packaging for XXXXXXXX and the *Required Advisory Statements for Medicine Labels* (RASML) document. In addition, the matter relating to the wording of the indication in the proposed CMI should be referred to this Section.

However, the Committee did not consider an Appendix H listing for pantoprazole as there was insufficient information available at the time to make an informed decision.

Schedule 3 – New entry

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

Schedule 4 – Amendment

PANTOPRAZOLE – amend entry to read:

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

Effective date – 1 March 2006

14.2 SUSDP, PART 5

14.2.1.1 ORLISTAT

PURPOSE

The Committee considered a submission to include orlistat in Appendix H of the SUSDP.

BACKGROUND

Orlistat is a potent, specific and reversible long-acting inhibitor of gastro-intestinal (GI) lipases which are required for the systemic absorption of dietary triglycerides. Orlistat selectively inhibits GI lipase activity within the GI tract and prevents the absorption of 30% of dietary fat, thus producing a weight loss effect. It is used in conjunction with dietary modification in the management of obesity.

Orlistat was first considered at the November 1999 NDPSC Meeting, when it was included in Schedule 4 (S4) following a recommendation by the Trans-Tasman Harmonisation Working Party. The May 2000 NDPSC Meeting noted that the December 1999 ADEC Meeting recommended approval to register XXXXXXXX containing orlistat XXX mg for the treatment of obese patients with a body mass index (BMI) ≥ 30 and overweight patients with a BMI ≥ 27 in the presence of other risk factors, in conjunction with a mildly hypocaloric diet. XXXXXXXX has been marketed in Australia by XXXXXXXX since XXXXXXXX.

Submissions to reschedule orlistat for the treatment of obesity from S4 to S3 were considered at both the June 2002 and February 2003 NDPSC Meetings. The February 2003 submission also sought to have orlistat included in Appendix H. On both these occasions, the Committee decided that the information submitted by the sponsor did not provide adequate evidence to address its concerns on its safety profile, the necessity for medical assessment to determine a patient's suitability for treatment with orlistat and the view that therapeutic intervention should not be the first-line treatment for obesity.

A third submission by XXXXXXXX to reschedule orlistat from S4 to S3 for the treatment of obesity, without inclusion in Appendix H, was considered by the October 2003 NDPSC Meeting. After considering the additional information provided by the sponsor and supporters, as well as the submissions expressing concern about the proposed rescheduling, the Committee agreed that its previous concerns had been adequately addressed and included orlistat for the treatment of obesity in S3. The Committee also noted that obesity is a disease which can be easily recognised by consumers and that pharmacists in Australia have good training and experience in providing advice and consultation in relation to management of weight loss and treatment of obesity.

The February 2005 NDPSC Meeting considered a proposal to include orlistat in Appendix H. The Committee noted that the NDPSC evaluation report had supported the proposal with the condition that reference to the modest efficacy and reduction of efficacy long-term seen in the clinical trial setting and potential side effects of orlistat need to be presented in any advertising for XXXXXXXX under the rubric of balanced, informed and non-misleading advertising. The evaluator had suggested statements such as the following to be made in any advertising for XXXXXXXX: *"Orlistat may only lead to minor weight loss in some people"*, *"Some people may experience side effects with orlistat particularly if diet is not adhered to"* and *"People may require vitamin replacement during orlistat therapy."* However, the Committee remained concerned that

omission of information in advertising campaigns about the modest efficacy and reduction of efficacy long-term seen in the clinical trial setting and potential side effects of orlistat could potentially create a consumer demand based on unrealistic expectations of the product's effectiveness. The Committee therefore did not support the proposal to include orlistat in Appendix H at that time.

DISCUSSION

Following the outcome of the February 2005 NDPSC Meeting, the sponsor submitted a further application seeking listing of orlistat in Appendix H. The Committee noted the following points which the sponsor highlighted in its application:

- If XXXXXXXX is requested by name, the consumer must be counselled by a pharmacist. This is in contrast to all other weight loss medication that can be purchased directly from a shop assistant.
- Pharmacist intervention could potentially result in referral to a general practitioner if underlying obesity related disorders are suspected and untreated. Access to most other weight loss medicines would allow these silent conditions to remain undiagnosed and untreated.
- There is the potential for improvement in obesity related risk factors by weight loss and direct effect from XXXXXXXX.
- XXXXXXXX is clinically proven and would result in improved health if used as intended.
- Given the provisions of the *Therapeutic Goods Advertising Code* (TGAC), the sponsor emphasised that XXXXXXXX advertising would not provide unrealistic expectations, mislead consumers, encourage inappropriate or excessive consumption or make "miraculous cure" claims but instead, be accurate, balanced, factual and be made only in conjunction to references to diet and exercise.

The Committee also noted the following comments provided by the sponsor in response to the concerns raised at the February 2005 NDPSC Meeting:

- The sponsor agreed that the statements suggested by the NDPSC evaluator were accurate and consistent with the TGAC.
- The Committee can impose conditions on an Appendix H listing by inclusion of the conditions in the SUSDP.
- If determined by the Committee to be necessary for Appendix H listing of orlistat, the sponsor agreed to include these specific statements in advertising for XXXXXXXX. As an indication of its willingness to adhere to the TGAC and the suggestions of the evaluator, the sponsor provided a statutory declaration signed by the Managing Director.

The Committee noted the following pre-meeting comments received:

- XXXXXXXX expressed a concern that, although any advertisements issued by the sponsor would comply with the TGAC, once consumers were exposed to branded advertisements, they would be more likely to have made their own assessment about their need and suitability for the product. Thus, consumers may be reluctant to accept further advice from pharmacists.
- XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX, XXXXXXXX and XXXXXXXX were all in support of an Appendix H listing for orlistat. All respondents contended that orlistat is the only clinically proven OTC weight loss medication not permitted to be brand advertised compared to other "unproven" OTC weight loss products available. As the current advertising restriction on XXXXXXXX is a barrier to counselling and supplying the product (eg. from XXXXXXXX submission which stated "pharmacist 'guessing' as to what the patient is asking for"), branded advertising would assist consumers and pharmacists in initiating a conversation about weight loss and possible treatment options and thus, increase community awareness of the weight management options available.
- XXXXXXXX further highlighted that once approval for listing in Appendix H was granted, the safeguard of pre-approval by XXXXXXXX for branded advertising of orlistat would apply. This pre-approval process was in place to ensure compliance with all aspects of the TGAC. In addition, the TGAC clause 4.1.1a requires an advertisement to comply with the common law of the Commonwealth, State and Territories. Thus, by including special conditions within the Appendix H, the application of TGAC clause 4.1.1a would ensure that any provisions contained in the SUSDP, when adopted in the State and Territory legislation, would be adhered to. However, including special conditions within Appendix H would duplicate existing regulatory mechanisms and be contrary to the principles-based approach established by the Therapeutic Goods Advertising Code Council (TGACC). Should the Committee consider the need to strengthen any of the principles of the TGAC, amendments can be proposed through the TGACC.

In light of XXXXXXXX's comment that its pre-approval process would ensure compliance with all aspects of the TGAC and thus would include any special conditions imposed through the SUSDP, members acknowledged the inaccuracy of the statement in the Record of Reasons of the February 2005 NDPSC Meeting *viz*, "Members understood that XXXXXXXX would assess the advertisement only for compliance with the TGAC and not for any other conditions imposed by the NDPSC".

The Committee also noted the letter from the TGACC to XXXXXXXX provided by the sponsor. The TGACC had considered that the present provisions of the principles-based Code were sufficiently robust in terms of effectively regulating the advertising of weight loss products. Members of the TGACC regarded that, of the conditions proposed by the NDPSC evaluator for Appendix H listing of orlistat, the proposed vitamin replacement

statement was product and substance specific which, although not covered specifically in the TGAC, would be enforceable under clause 4.1.1a.

XXXXXXXX of the TGA's Non-Prescription Medicines Branch, which encompasses the Advertising Section, presented an invited overview of the TGACC to the Committee. XXXXXXXX did not address the question of the appropriateness of Appendix H listing of orlistat. Members noted that there were proposals to amend the TGAC to create an advertising Code for both Australia and New Zealand. Members were also informed that there was a proposal to change the TGAC regarding the weight management category (clause 7.3) to ensure a balance between claims and appropriate diet and lifestyle messages.

A discussion on the criteria for an Appendix H listing took place. Overall, members recognised that successful and long term weight loss in obese patients is desirable and has undoubted public health benefits. Members noted a commitment from XXXXXXXX to undertake the advertising of orlistat responsibly. Nonetheless, the Committee remained unconvinced that branded advertising of orlistat would not lead to inappropriate use of the medication by vulnerable individuals. In particular, several members raised concerns that advertising of orlistat could be perceived as a first-line therapy in weight loss rather than the recommended lifestyle changes involving diet, exercise and behavioural therapy. By substituting effective forms of first-line therapies with orlistat, branded advertising of orlistat may promote unreasonable and unrealistic expectations of the effectiveness of pharmacotherapy in weight loss, particularly since the available clinical data on orlistat suggested modest efficacy and reduced long-term efficacy. Additionally, branded advertising may potentially create an increase in consumer demand of the product based on unrealistic expectations of the product's effectiveness. Members were concerned that under these circumstances, consumers were less likely to be influenced by the pharmacist's assessment of the suitability of the product for the individual consumer. As such, members considered that orlistat was not suitable for branded advertising.

OUTCOME

The Committee did not support the inclusion of orlistat in Appendix H. The Committee remained concerned that branded advertising of orlistat would convey an inappropriate public health message that pharmacotherapy is the first-line treatment for obesity or over-weight conditions, and could expose the public to unnecessary risks. Additionally, it was considered that branded advertising was likely to increase consumer expectations making them less likely to be influenced by the pharmacist's assessment in determining the suitability of the product for the individual consumer. The Committee reaffirmed its view that consumers should be encouraged to undertake appropriate lifestyle changes as a first-line option to achieve safe and long-term weight loss.

14.2.1.2 DIPHENHYDRAMINE

PURPOSE

The Committee considered a submission to include diphenhydramine for the treatment of symptoms of coughs, colds and influenza in Appendix H of the SUSDP.

BACKGROUND

For many years, diphenhydramine and other sedating antihistamines were classified as Schedule 2 (S) medicines when in oral preparations for use in those aged two years and older and containing one or more of the following substances: an antitussive other than codeine or dihydrocodeine, an expectorant, phenylephrine or pseudoephedrine.

The February 2004 NDPSC Meeting amended the S2 entries for oral sedating antihistamines including diphenhydramine to address the concerns of the sedating effects of the antihistamines and to harmonise scheduling with New Zealand. As a result, oral preparations for the treatment of symptoms of coughs, colds or influenza when combined with a sedating antihistamines were classified as S2 when at least one of the other therapeutically active substances was a sympathomimetic decongestant or when in a day-night pack with the dose containing the sedating antihistamine was labelled for bed-time use. All other oral preparations for the treatment of symptoms of coughs, colds or influenza that contain oral sedating antihistamines when combined with at least one therapeutically active substance that was not a sympathomimetic decongestant were rescheduled to S3. This amendment was given effect from 1 September 2004.

Following the amendment to the SUSDP, XXXXXXXX submitted a proposal to the February 2005 NDPSC Meeting to amend the S2 entry for diphenhydramine to allow products for the treatment of symptoms of coughs, colds or influenza that do not contain a sympathomimetic decongestant (such as an antitussive or an expectorant) as at least one of the therapeutically active substances when in combination with diphenhydramine to remain in S2 while retaining hypnotic preparations in S3. However, the Committee instead foreshadowed the consideration of the scheduling of all oral sedating antihistamines relating to any outcomes on this issue from the June 2005 meeting of the New Zealand's Medicines Classification Committee in anticipation of maintaining Trans-Tasman scheduling harmonisation of these medicines. (See item 18.1.1)

DISCUSSION

XXXXXXXX submitted a proposal to include in Appendix H oral preparations in S3 containing diphenhydramine for the treatment of symptoms of coughs, colds or influenza when at least one of the other therapeutically active substances is not a sympathomimetic decongestant. The Committee noted the following points highlighted by the sponsor in the submission:

- Diphenhydramine is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold.
- In Australia, diphenhydramine has been used in oral preparations for the treatment of symptoms of coughs, colds or influenza for many years and have been advertised and promoted to consumers. Continued advertising of diphenhydramine oral preparations for the treatment of such symptoms has not, and is not expected to lead to inappropriate patterns of medication use.
- The sponsor is not aware of any evidence of abuse of these oral preparations used for the treatment of symptoms of coughs, colds or influenza.
- Advertising would be expected to maintain or raise the level of consumer knowledge about various oral treatments available for the relief of symptoms of coughs, colds or influenza.
- Advertising would direct consumers to pharmacists and healthcare professionals who are able to provide the best advice on the condition and treatment options, and who can direct consumers to a doctor if required.

Following assessment of the submission, the Committee noted that the Secretariat's evaluation report highlighted the following points in support of the submission:

- Advertising of S3 diphenhydramine would be for the treatment of symptoms of coughs, colds or influenza.
- Prior to the rescheduling, all S2 oral preparations containing sedating antihistamines for the treatment of symptoms of coughs, colds and influenza with or without a sympathomimetic decongestant were allowed to be advertised for many years.
- A literature search revealed that diphenhydramine has a minimal risk of abuse and that multiple reports of abuse were associated with single active formulations.
- An Appendix H listing of S3 diphenhydramine for the treatment of symptoms of coughs, colds or influenza would support and reinforce the role of the pharmacist as such products would be provided to consumers with the direct involvement of the pharmacist.

The Committee noted the pre-meeting comments received from XXXXXXXX, XXXXXXXX and XXXXXXXX. The respondents were firmly opposed to the advertising of diphenhydramine when indicated for sleep disorders which may lead to an increase in the inappropriate use or abuse of diphenhydramine.

The Committee acknowledged that oral preparations containing sedating antihistamines for the treatment of symptoms of coughs, colds and influenza without a sympathomimetic decongestant had been in S2, and thus permitted to be advertised, for many years. However, members highlighted that such preparations were rescheduled from S2 to S3 due to concerns on the potential risks associated with the sedative effects of the antihistamines. Furthermore, these S3 preparations did not contain one other therapeutically active ingredient that would antagonise the sedative effects. A member

also expressed that as Pharmacist Only Medicines, it should be up to the assessment of the pharmacist to determine the appropriate S3 product for an individual consumer.

Given the public health concerns on the potential risks associated with sedation, members held the view that advertising of S3 diphenhydramine for the treatment of symptoms of coughs, colds and influenza was not appropriate.

OUTCOME

The Committee agreed not to include diphenhydramine for the treatment of symptoms of coughs, colds and influenza in Appendix H. Members considered that it was not appropriate to advertise S3 diphenhydramine because of public health concerns on the potential risks associated with the sedative effects of diphenhydramine.

14.2.2 APPENDIX K

14.2.2.1 AMISULPRIDE

PURPOSE

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

BACKGROUND

Amisulpride is an atypical antipsychotic of the benzamide class. It is indicated for the treatment of acute and chronic schizophrenic disorders in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

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

[Paragraph deleted]

The February 2005 NDPSC Meeting included aripiprazole, an atypical antipsychotic for the treatment of schizophrenia, in Appendix K on safety grounds that there was a potential for aripiprazole to cause sedation during the first week of treatment and that the sedative effect would be similar to that of risperidone, which was listed in Appendix K. During the course of the Committee's consideration, members were provided with a summary of the sedation potential of atypical antipsychotics and haloperidol, a conventional antipsychotic, based on the information from existing Product Information (PI) documents and listing in Appendix K. It was highlighted that although the summary showed that the sedation potential for amisulpride was 3% compared with 4% in

haloperidol, which was listed in Appendix K, and 0% in placebo, amisulpride was not listed in Appendix K. The Committee thus foreshadowed the inclusion of amisulpride in Appendix K.

DISCUSSION

The Committee noted the article by Miller from *Prim Care Companion J Clin Psychiatry 2004;6[suppl 2]:3-7* which stated that studies have indicated that the sedative effect of antipsychotics was related to the dosage and affinity of the antipsychotics for histamine H1 receptors.

The Committee also noted the following information from the current approved PI for XXXXXXXX (amisulpride) regarding sedation and alcohol:

- Under *Pharmacology* – Amisulpride displays low affinity for histamine receptor subtypes.
- Under *Adverse Reactions* – In controlled clinical trials, somnolence occurred in 3% of amisulpride-treated patients (n=921) compared to 0% in the placebo group (n=202), 4% in the haloperidol group (n=245) and 4% in the combined flupentixol and risperidone group (n=62).
- Under *Effects on ability to drive and use machines* – "Even used as recommended, amisulpride may affect reaction time so that the ability to drive vehicles or operate machinery can be impaired."
- Under *Interactions* – "Amisulpride may enhance the effects of alcohol…CNS depressants…"

In addition, the Committee noted that the Consumer Medicine Information (CMI) for XXXXXXXX included the warning "XXXXXXXX may cause drowsiness in some people. Be careful driving or operating machinery until you know how XXXXXXXX affects you…The effects of alcohol could be made worse while taking XXXXXXXX. It is not recommended that you drink alcohol while taking XXXXXXXX … XXXXXXXX can increase drowsiness caused by medicines affecting your nervous system."

[Section deleted]

Members were informed that amisulpride was included in the list of medicines contained in the Pharmaceutical Society of Australia's publication *Australian Pharmaceutical Formulary and Handbook 19th Edition* (APF-19) required to be labelled with ancillary label 1 "This medicine may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery."

The Committee noted the pre-meeting submission received from XXXXXXXX, the sponsor for amisulpride, opposing the proposal to include amisulpride in Appendix K due to the following reasons:

- Results of human pharmacodynamic studies which examined the effects of amisulpride on psychomotor performance, body sway and information processing consistently demonstrated that amisulpride in doses of 50 to 400 mg did not impair performance in a controlled, double-blind, randomised study settings. These studies were submitted as part of the application to register amisulpride in Australia.
- The incidence of sedation with amisulpride would be expected to be low due to its pharmacological profile which showed strong affinity only for the dopamine D2 and D3 receptors.
- An article by Keks from the *Australian Prescriber 2004;27:146-149,* which was provided with the submission, included a tabulation of the relative frequency of common adverse effects of antipsychotics at usual therapeutic doses. The tabulation indicated that sedation was infrequently reported for amisulpride when compared with clozapine, olanzapine and quetiapine.
- Based on the available data, the sponsor was of the view that amisulpride did not warrant inclusion in Appendix K and requested that the Committee consider a hierarchal approach to the inclusion of atypical antipsychotics into Appendix K.

OUTCOME

The Committee found it difficult to evaluate the sedation potential of amisulpride. A concern was expressed that inclusion of a substance in Appendix K that may not cause drowsiness would dilute the importance of the sedation warning label.

Due to the conflicting information from the available data, PI and CMI documents for amisulpride relating to its sedation potential, the Committee agreed to defer consideration of this matter and seek expert advice from ADEC.

14.2.2.2 CLOZAPINE

PURPOSE

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

BACKGROUND

Clozapine, a tricyclic dibenzodiazepine derivative, is an atypical antipsychotic indicated for the treatment of schizophrenia in those patients who are non-responsive to, or intolerant of, other antipsychotic medicines.

At the November 1972 meeting, the Committee included clozapine in Schedule 4. The Committee then included clozapine in Appendix D at the November 1992 meeting to restrict its supply through authorised medical practitioners following consideration of the June 1992 ADEC Meeting which recommended approval for the registration of clozapine

on the proviso that patients undergoing treatment with clozapine must undergo regular monitoring of their white cell counts on the grounds of its propensity to cause agranulocytosis.

The February 2005 NDPSC Meeting included aripiprazole, an atypical antipsychotic for the treatment of schizophrenia, in Appendix K on safety grounds that there was a potential for aripiprazole to cause sedation during the first week of treatment and that the sedative effect would be similar to that of risperidone, which was listed in Appendix K. During the course of the Committee's consideration, members were provided with a summary of the sedation potential of atypical antipsychotics and haloperidol, a conventional antipsychotic, based on the information from existing Product Information (PI) documents and listing in Appendix K. It was highlighted that although the summary showed that the overall incidence of sedation for clozapine was about 40%, clozapine was not listed in Appendix K. The Committee thus foreshadowed the inclusion of clozapine in Appendix K.

DISCUSSION

The Committee noted the article by Miller from *Prim Care Companion J Clin Psychiatry 2004;6[suppl 2]:3-7* which stated that studies have indicated that the sedative effect of antipsychotics was related to the dosage and affinity of the antipsychotics for histamine H1 receptors.

The Committee also noted the following information from the current approved PI for XXXXXXXX (clozapine) regarding sedation and alcohol:

- Under *Pharmacology*: Clozapine has potent antihistaminic effects and that clinically, Clozaril produces rapid and marked sedation, and exerts antipsychotic effects.
- Under *Adverse Reactions* – Nervous system disorders: "Very common (≥ 10%): fatigue/drowsiness/sedation (overall incidence about 40%), dizziness."
- Under *Interactions with Other Drugs* – "XXXXXXXX may enhance the central effects of alcohol, MAO inhibitors and CNS depressants…"

In addition, the Committee noted that the Consumer Medicine Information (CMI) for XXXXXXXX included the warnings "Be careful driving or operating machinery until you know how XXXXXXXX affects you. As with other antipsychotic medicines, XXXXXXXX may cause tiredness, drowsiness, dizziness, fainting or seizures (fits) in some people, especially at the start of treatment. Make sure you know how you react to XXXXXXXX before you drive a car, operate machinery or do anything else that could be dangerous. Be careful when drinking alcohol…while you are taking XXXXXXXX. XXXXXXXX can increase the drowsiness caused by alcohol…"

[2 Paragraphs deleted].

Members were informed that clozapine was included in the list of medicines in the Pharmaceutical Society of Australia's publication *Australian Pharmaceutical Formulary and Handbook 19th Edition* (APF-19) required to be labelled with ancillary label 1: "This medicine may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery."

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

- XXXXXXXX, the sponsor for XXXXXXXX, had no objection to the foreshadowed decision to include clozapine in Appendix K as this was consistent with the approved PI for XXXXXXXX.
- XXXXXXXX, the sponsor for amisulpride, supported the proposal to include clozapine in Appendix K. XXXXXXXX also provided a paper by Keks from *Aust Prescr 2004;27:146-149* which included a tabulation of the relative frequency of common adverse effects of antipsychotics at usual therapeutic doses. The tabulation indicated that clozapine had a higher incidence of sedation when compared to amisulpride.

DECISION 2005/44 - 25

On the basis of the available information which showed that sedation was a prominent side effect of clozapine, the Committee agreed with the foreshadowed decision to include clozapine in Appendix K of the SUSDP.

Appendix K - New entry

Clozapine

14.2.2.3 QUETIAPINE

PURPOSE

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

BACKGROUND

Quetiapine is a dibenzothiazepine atypical antipsychotic which is structurally related to olanzapine and clozapine.

The NDPSC August 1999 Meeting included quetiapine in Schedule 4 following a recommendation from the 4th Meeting of the Trans-Tasman Harmonisation Working Party.

The NDPSC February 2000 Meeting noted the recommendation from the October 1999 ADEC Meeting of approval of the application to register XXXXXXXX containing XXX mg, XXX mg and XXX mg of quetiapine as fumarate for the treatment of schizophrenia.

The February 2005 NDPSC Meeting included aripiprazole, an atypical antipsychotic for the treatment of schizophrenia, in Appendix K on safety grounds that there was a potential for aripiprazole to cause sedation during the first week of treatment and that the sedative effect would be similar to that of risperidone, which was listed in Appendix K. During the course of the Committee's consideration, which also included the advice of XXXXXXXX, the Committee was provided with a summary of the sedation potential of atypical antipsychotics and haloperidol, a conventional antipsychotic, based on the information from existing Product Information (PI) documents and listing in Appendix K. It was highlighted that quetiapine was not included in Appendix K although the summary showed that the sedation potential for quetiapine was very common (≥ 10%) usually during the first two weeks of treatment and generally resolved with continued administration), and that the XXXXXXXX advice highlighted that aripiprazole was less sedating than quetiapine which was a relatively sedating antipsychotic drug. The Committee thus foreshadowed the inclusion of quetiapine in Appendix K.

DISCUSSION

The Committee noted the article by Miller from *Prim Care Companion J Clin Psychiatry 2004;6[suppl 2]:3-7* which stated that studies have indicated that the sedative effect of antipsychotics was related to the dosage and affinity of the antipsychotics for histamine H1 receptors.

The Committee also noted the following information from the current approved PI for XXXXXXXX (quetiapine) regarding sedation:

- Under *Pharmacology* – Quetiapine has high affinity at histaminergic receptors.
- Under *Adverse Reactions* – Very common (≥ 10%): somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of Seroquel.
- Under *Effects on ability to drive and use machines* – "Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Patients likely to drive or operate other machines should therefore be cautioned appropriately."

In addition, the Committee noted that the Consumer Medicine Information (CMI) for XXXXXXXX included the warning "XXXXXXXX can make some people dizzy or sleepy. Make sure you know how you react to XXXXXXXX before you do anything that could be dangerous if you are dizzy or sleepy." It was highlighted that although the PI did not mention any precaution on alcohol, the CMI had the warning "Be careful when drinking alcohol while you are using XXXXXXXX. It may make you dizzy or sleepy."

[Section deleted].

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

- XXXXXXXX, the sponsor for quetiapine, was against the proposal to include quetiapine in Appendix K. The sponsor contended that the data presented to the TGA during the registration process demonstrated that the sedative effect of quetiapine generally resolved usually within the first two weeks of treatment and was not a continuous side effect. As this information already existed in the PI and CMI documents for quetiapine, the sponsor argued that it was unnecessary to add an additional warning on the labelling, particularly in light of its transient sedative effect.
- XXXXXXXX, the sponsor for amisulpride, supported the proposal to include quetiapine in Appendix K. XXXXXXXX also provided a paper by Keks from *Aust Prescr 2004;27:146-149* which included a tabulation of the relative frequency of common adverse effects of antipsychotics at usual therapeutic doses. The tabulation indicated that quetiapine, olanzapine and clozapine had similar incidences of sedation and that quetiapine had a higher incidence of sedation when compared to amisulpride.

DECISION 2005/44 - 26

On the basis of the available information, the Committee agreed with the foreshadowed decision to include quetiapine in Appendix K of the SUSDP on the grounds that there was a potential for quetiapine to cause sedation during the first two weeks of treatment.

Appendix K - New entry

Quetiapine

14.2.3 APPENDIX A

14.2.3.1 BLOOD PRODUCTS

PURPOSE

The Committee considered the foreshadowed decision to include blood products in Appendix A of the SUSDP to exempt such products from the requirements of scheduling.

BACKGROUND

Historically, the Committee had a standing policy of not scheduling blood products when their use outside of the clinical or hospital settings was unlikely. The Committee held the view that scheduling such products would place unwarranted and potentially excessive restrictions when the supply and safe use of such products could be adequately controlled through other mechanisms.

The May 2001 NDPSC Meeting considered the scheduling of a recombinant Factor VIII product, octocog alfa. The Committee agreed that its safety profile was consistent with similar blood products already exempt from scheduling. The Committee also noted that at that time, recombinant Factor VIII was classified as Pharmacy Only medicine in New Zealand. Furthermore, the Committee agreed to consider in detail a proposal to include a general exemption for blood products for therapeutic use in Appendix A of the SUSDP to reflect the Committee's policy of not scheduling blood products for supply or use in clinical or hospital settings when the outcomes of the Review of the Australian Blood Banking and Plasma Product Sector (the Review) became available.

The final report of the Review was subsequently released in 2001. The February 2005 NDPSC Meeting considered the Review and was satisfied that there were regulatory mechanisms in place to warrant the exclusion of blood products from the SUSDP *viz,* at the State/Territory level in managing the use of blood and blood products in institutions in which blood transfusion services were provided, at the national level as administered by the National Blood Authority (NBA) in managing and overseeing the national blood supply and the TGA in regulating the safety, efficacy and quality of blood products. The Committee thus foreshadowed the inclusion of blood products in Appendix A to exempt such products from the requirements of scheduling. It was also agreed that the proposed exclusions to this entry were for blood derived products that contain substances appropriate for scheduling and those already included in the Schedules which the Committee wished to remain subject to scheduling requirements as appropriate. The Committee also confirmed its view that future amendments to the proposed Appendix A entry would be considered on a case-by-case basis according to the normal procedures of the NDPSC.

DISCUSSION

Following the February 2005 NDPSC Meeting, comments relating to the foreshadowed decision were sought from XXXXXXXX, XXXXXXXX, and XXXXXXXX.

The Committee noted the following comments from XXXXXXXX:

- The DSEB regulates products derived from human plasma (eg. coagulation factors, immunoglobulins and albumin) but not whole blood or blood components (eg. packed cells and platelets).
- If the Committee’s intention was to exempt only those products derived from human blood as foreshadowed, this would mean that recombinant products would not be exempted. However, exempting one Factor VIII product derived from human plasma and not the other comparable Factor VIII recombinant product, solely on the basis of the method of manufacture, seemed to be illogical. In addition, Factor VIIa is only available in Australia as a recombinant product.
- Previously, most plasma-derived products were being manufactured from Australian blood by XXXXXXXX and distributed free of charge by the ARCBS, which was the national organisation responsible for the provision of quality blood products, tissues

and related services in Australia. In recent years, a number of foreign products were registered in Australia (eg. immunoglobulins and recombinant coagulation factors) which were commercially available direct from sponsor companies, as with any registered pharmaceuticals, and that the number of these foreign blood products on the Australian market was likely to increase in the future.

- As plasma-derived products are intended for the treatment of serious diseases, require supervision by a medical practitioner and are not universally subject to controls by the Commonwealth and States/Territories that would obviate the need for scheduling, these products should not be exempted from scheduling.

The Committee noted the following interim response from the XXXXXXXX pending endorsement by XXXXXXXX:

- Blood products should not be exempted from scheduling as the prescription of a blood component, blood derivative or a medical device incorporating a blood component or product should rest with a medical practitioner.
- In New Zealand, all blood components and products were regulated as medicines requiring a prescription by a medical practitioner with the exception of midwives who were able to prescribe anti-RhD immunoglobulin.

The Committee was further advised that XXXXXXXX, at its recent meeting, had endorsed the comments from XXXXXXXX and XXXXXXXX. Thus, the consolidated view of XXXXXXXX was that blood, blood components, plasma-derived products and the recombinant derivatives of these products should be classified as Schedule 4 (S4).

The Committee also noted the comment from XXXXXXXX which was supportive of the proposal to exempt blood products, including those derived through the fractionation of plasma, from the requirements of scheduling. XXXXXXXX stated that the proposed exemption would have a minimal direct impact on its organisation.

Members were informed that there were no pre-meeting submissions received.

The Committee discussed the current arrangement relating to the supply of whole blood and blood components in Australia. For many years, whole blood and blood components were being supplied by or on the order of medical practitioners without having to be dispensed by pharmacists. Moreover, hospitals and health services have policies and guidelines in place to ensure best practice in the supply and use of blood and blood products. There was also no evidence to suggest that the current arrangement was not feasible and therefore would need the incorporation of such products into State and Territory drugs/poisons legislation. As such, members agreed that XXXXXXXX's concern that whole blood and blood components should be classified as S4 was already being addressed through current arrangement without the involvement of a pharmacist. Furthermore, members agreed that it would be inappropriate and impractical for a pharmacist to be required to dispense whole blood and blood components particularly in an emergency setting. Overall, the Committee agreed that whole blood and blood components should remain unscheduled.

However, the Committee was conscious of the recent shift in the supply arrangements of plasma-derived products, which now included foreign blood products, and the increase in the manufacture of comparable recombinant products. The Committee therefore agreed to foreshadow the consideration of the scheduling of all products derived from the fractionation of plasma and comparable recombinant products at the October 2005 meeting since it considered that there should be a consistent approach in the scheduling of these products, regardless of the manufacturing method.

The Committee also discussed an appropriate definition for blood and blood components. It was noted that the *Therapeutic Goods Act 1989* (the Act) defined 'blood' as "whole blood extracted from human donors" and that 'blood components' meant "therapeutic components that have been manufactured from blood (including red cells, white cells, stem cells, platelets and plasma), except for products produced through fractionation of plasma." Members agreed that the SUSDP definitions for blood and blood components should be consistent with those as defined in the Act.

OUTCOME

Due to the recent shift in the supply arrangements of plasma-derived products, which included foreign blood products, and the increase in the availability of recombinant derivatives, the Committee agreed to foreshadow the consideration of the scheduling at the October 2005 meeting of those products derived from the fractionation of plasma and comparable recombinant products that are currently not scheduled.

DECISION 2005/44 - 27

On the basis of the available information, the Committee agreed to include in Appendix A of the SUSDP an entry for whole blood and blood components for the exemption of such products from the requirements of scheduling. Members were satisfied that the existing mechanisms in place at a State/Territory level and at a national level as administered by the NBA in managing and overseeing the national supply of whole blood and blood components were appropriate.

Part 1, Interpretation – New Entry

"Blood" means whole blood extracted from human donors.

"Blood components" means therapeutic components that have been manufactured from blood (including red cells, white cells, stem cells, platelets and plasma), except for products derived through fractionation of plasma.

Appendix A - New entry

Whole blood and blood components **except** when separately specified in these Schedules.

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

15.1 NEW SUBSTANCES (NOT SEEN BEFORE BY THE NDPSC)

15.1.1 LARONIDASE - RCH

DECISION 2005/44 – 28

The Committee agreed that laronidase be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and that safe use required patient management and monitoring by a medical professional. The inclusion of laroniodase in Schedule 4 would also harmonise the scheduling with New Zealand.

Schedule 4 – New entry

LARONIDASE.

15.1.2 ARTICAINE

DECISION 2005/44 - 29

The Committee agreed to include articaine in Schedule 4 of the SUSDP on the grounds that the safe use of the medicine required patient management and monitoring by a dental professional. A Schedule 4 classification also allowed harmonisation with New Zealand.

Schedule 4– New entry

ARTICAINE.

15.1.3 DARIFENACIN HYDROBROMIDE

DECISION 2005/44 - 30

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

Schedule 4 – New entry

DARIFENACIN.

15.1.4 EVEROLIMUS

DECISION 2005/44 - 31

The Committee agreed that everolimus be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and that safe use required patient management and monitoring by a medical professional. Inclusion in Schedule 4 would also harmonise with New Zealand.

Schedule 4 – New entry

EVEROLIMUS.

15.1.5 OCTOCOG ALFA

OUTCOME

The Committee deferred consideration of this item to the October 2005 meeting when a policy position on the scheduling of blood products would be further considered by the Committee.

15.1.6 BEVACIZUMAB

DECISION 2005/44 - 32

The Committee agreed that bevacizumab be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of the medicine required patient management and monitoring by a medical professional. The inclusion of bevacizumab also allowed harmonisation with New Zealand.

Schedule 4 – New entry

BEVACIZUMAB.

15.1.7 CETUXIMAB

DECISION 2005/44 - 33

The Committee agreed that cetuximab be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of the medicine required patient management and monitoring by a medical professional.

Schedule 4 – New entry

CETUXIMAB.

15.1.8 CINACALCET

DECISION 2005/44 - 34

The Committee agreed to include cinacalcet in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and safe use of the medicine required patient management and monitoring by a medical professional. Inclusion in Schedule 4 also harmonised the scheduling with New Zealand.

Schedule 4 – New entry

CINACALCET.

15.1.9 NORELGESTROMIN

DECISION 2005/44 - 35

The Committee agreed that norelgestromin should be included in Schedule 4 of the SUSDP on the grounds that the safe use of the medicine required patient management and monitoring by a medical professional.

Schedule 4 – New entry

NORELGESTROMIN.

15.1.10 PORACTANT ALFA

DECISION 2005/44 - 36

The Committee agreed that poractant alfa be included in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and that safe use required patient management and monitoring by a medical professional. Inclusion in Schedule 4 would also harmonise with New Zealand.

Schedule 4 – New entry

PORACTANT ALFA.

15.1.11 PREGABALIN

DECISION 2005/44 - 37

The Committee agreed that pregabalin be included in Schedule 4 of the SUSDP on the basis that the condition being treated necessitated appropriate medical diagnosis and that safe use required patient management and monitoring by a medical professional.

The Committee further agreed that pregabalin also be included in Appendix K on the basis that there was potential for pregabalin to have a sedative effect.

Inclusion in Schedule 4 would achieve harmonisation with New Zealand.

Schedule 4 – New entry

PREGABALIN.

Appendix K – New Entry

Pregabalin.

23. AMENDMENTS TO THE SUSDP

23.1.1 FOR INFORMATION – MINOR EDITORIAL CHANGES AND ERRATA IN SUSDP 20

PURPOSE

The Committee noted the inclusion of minor editorial corrections made to SUSDP 20 identified by the Secretariat during consolidation of the SUSDP No. 19 and its three amendments.

DISCUSSION

The Committee noted that the following editorial changes have been made to SUSDP 20:

- The age expressions written in words (e.g. six years of age or less) rather than the number (e.g. 6 years of age or less) in SUSDP 19 Amendments 1 & 2 was amended to the numerical version in SUSDP 20 for consistency with the majority of existing entries in the Schedules.
- Appendix B formatting was slightly altered for clarity through addition of an indent where an entry goes to a second line. Additionally, all months in the “date of entry” column have been constrained to the first 3 letters of the month name.

- The reference to tea-tree oil in the S6 entry for melaleuca oil was changed from all uppercase to all lowercase for consistency with most common name references to read:

MELALEUCA OIL (tea-tree oil) **except**:

(a) when packed in containers having a nominal capacity of 15 mL or less fitted with a restricted flow insert, and labelled with the warnings:

KEEP OUT OF REACH OF CHILDREN; and

NOT TO BE TAKEN;

(b) when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and child-resistant closure, and labelled with the warnings:

KEEP OUT OF REACH OF CHILDREN; and

NOT TO BE TAKEN; or

(c) in preparations containing 25 per cent or less of melaleuca oil.

- The existing spelling in the Schedule 5 entry for TDE [1,1-dichloro-2,2-bis(4-chlorophenyl)ethane] was rebracketted to read:

TDE (1,1 dichloro-2,2-bis[4-chlorophenyl]ethane) in preparations containing 10 per cent or less of TDE.

- The existing spelling in the Schedule 6 entry C<u>H</u>LOTHIANDIN was corrected to remove an inadvertent H to read:

CLOTHIANDIN

- The existing o-Dichlorobenze entry in Appendix E Part 2 was replaced with ortho-Dichlorobenzene and the entries for para-Dichlorobenzene have been inserted in Appendix E Part 2 and Appendix F Part 3 and the existing PDB entries cross referenced in the index. Additionally, the existing Appendix F Part 3 entry for "Nicotine except when in tobacco or Schedule 2" has been replaced with "Nicotine except when in tobacco or when included in Schedule 2" for clarity. The Committee further noted that the existing spelling in the Appendix F Part 3 entry "1-(B-Methyl sulphonamideethyl)-2-amino-3-N,N-diethylaminobenzene" has been corrected to "1-(beta-Methyl sulphonamidoethyl)-2-amino-3-N,N-diethylaminobenzene". These changes read as follows:

Appendix E Part 2

POISON .....**STANDARD STATEMENTS**

ortho-Dichlorobenzene A,G3,E1,S1

para-Dichlorobenzene (PDB).....A

Appendix F Part 3

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**
para-Dichlorobenzene		1,4
1-(beta-Methyl sulphonamidoethyl)-2-amino-3-N,N-diethylaminobenzene		1,4,8
Nicotine **except** when in tobacco or when included in Schedule 2.....		1,4

- The Appendix E Introduction "Poisons Information Centre Telephone Numbers" paragraph was been amended for consistency with Appendix F Introduction to read:

Appendix E and F Introduction

Poisons Information Centre Telephone Numbers

Companies should use the poisons information centre telephone number(s) appropriate to the country(ies) of sale for the product, that is Australia or New Zealand or both. These are 13 1126 for Australia and free-call number 0800764766 for New Zealand.

Companies wishing to use a poisons information centre telephone number other than the national telephone numbers for Australia and New Zealand must meet the following criteria:

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

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

The Committee also noted that the following entries have been moved for consistency:

- The Schedule 9 entry for N,α-dimethyl-3,4-(methylenedioxy)phenylethylamine ∗(MDMA) has been alphabetised under “D” from the existing “N”.
- The Appendix B entries for n-Butyl Butyrate and n-Butyl Lactate have been alphabetised under “B” from the existing “n”.
- The Schedule 5 entry for para-DICHLOROBENZENE was moved to correspond alphabetically to “D” from the existing “p”.