Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

58th Meeting
16-17 February 2010

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNPM	Advisory Committee on Non-Prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	see ACPM
ADI	Acceptable Daily Intake
ADR	Adverse Drug Reaction
ADRAC	see ACSM
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

CACC	Combination Analgesic Containing Codeine
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	see ACCM
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments
CRC	Child-Resistant Closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority (NZ)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GORD	Gastro-oesophageal Reflux Disorder
GP	General Practitioner
HCN	Health Communication Network

INCB	International Narcotics Control Board
INN	International Non-proprietary Name
ISO	International Standards Organization
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
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MCC	Medicines Classification Committee (NZ)
MEC	see ACNPM
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
NOAEL	No Observed Adverse Effect Level
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health
ODBT	Office of Devices, Blood and Tissues
OLSS	Office of Laboratories and Scientific Services

OOS	Out of Session
OPM	Office of Prescription Medicine
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
PSC	Poisons Schedule (Standing) Committee (now NDPSC)
PSCC	Poisons Schedule Sub-Committee (now NDPSC)
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted Flow Insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines 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
USFDA	United States Food and Drug Administration
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1. PRELIMINARY MATTERS

1.6 PROCEDURAL MATTERS

No items.

1.7 NDPSC WORKING PARTIES

No items.

1.8 PROPOSED ROUTINE CHANGES TO THE SUSDP

No items.

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 APPROVED NAME

PURPOSE

The Committee considered the definition for "approved name".

BACKGROUND

At the October 2008 meeting, the Committee was asked to consider whether or not all reference sources listed under the "approved name" entry in Part 1, Interpretation, were still warranted. The Committee agreed to defer consideration pending advice from the TGA, APVMA and NICNAS.

At the February 2009 meeting, the Committee noted advice that had been received to date. It was suggested that this item be passed to the Committee's Drafting Advisory Panel (DAP) to determine the appropriate references to be included under 'approved name'. This issue was not tabled at the June 2009 meeting as it was still under consideration by DAP.

At the October 2009 meeting, the Committee decided to foreshadow an amendment to the definition for "approved name" to include:

- reference to the TGA with regard to naming of poisons for human therapeutic use;
- reference to the APVMA with regard to naming of poisons for animal or agricultural use; and

- a number of amendments and updates as recommended by the Drafting Advisory Panel for other scheduled substances.

DISCUSSION – SUBMISSIONS

October 2009 discussion

Members recalled the following regarding the DAP's recommendations for approved names for chemicals not regulated by the TGA or APVMA:

Current references that remain relevant (slight updates as necessary to names etc.)

- (b)(i) The English name recommended by Standards Australia.
- (b)(ii) The English name given by the International Organization for Standardization.
- (b)(iii) The English name given by the British Standards Institution (BSI).
- (b)(vii) The international non-proprietary name recommended by WHO.
- (b)(viii) The accepted scientific name or the name descriptive of the true nature and origin of the poison.

Current references proposed to be replaced/deleted/extended

- (b)(iii) There were ongoing moves to harmonise standards in Europe and as such some British Standards were gradually being superseded or replaced by the relevant European Standards (EN). It was suggested that the English name given by the European Standards (http://www.cen.eu/cenorm/homepage.htm) would be an appropriate addition to the approved name list.
- (b)(iv) The Australian Approved Name; (b)(v) the English name in the British Pharmacopoeia, the British Pharmaceutical Codex, the Australian Pharmaceutical Formulary and Handbook or the British Pharmacopoeia (Veterinary); (b)(vi) the approved name by the Medicines Commission of Great Britain. It was proposed that these be replaced by reference to the approved name for human therapeutic use, animal use or agricultural use.

Proposed new references

- Noting the ACCC requirements for naming cosmetics, it was suggested that the International Nomenclature Cosmetic Ingredient name would be an appropriate addition to the approved name list.
- Finally, it was suggested that the Committee consider that the name used for an entry in the SUSDP schedules should also have the status of an approved name. It was further suggested that this actually be the first name in the hierarchy since this is the name which had been actively considered and agreed to by the Committee.

Members also recalled the DAP's suggested approaches to the "approved name" for regulated substances:

- Firstly, the Committee could consider updating the references in the current "approved name" definition to include those authoritative reference sources as provided by the TGA and APVMA together with those suggested by DAP for scheduled ingredients in unregulated products.
- Alternatively, the Committee could use this opportunity to leave the task of maintaining references for approved name to the appropriate regulator for those use patterns with a clearly defined regulator (TGA and APVMA). In this case the need to directly cite references may only be necessary for unregulated chemicals.

The Committee's response to the DAP's suggestions included:

- Members discussed whether to leave the task of maintaining the approved name references for medicines and agvet products to the TGA and APVMA. It was generally agreed that this was the best approach as it ensured that there was consistency with the regulators while avoiding the unnecessary work load which would result should the Committee have to maintain a duplicate of these references in the SUSDP.
- Members also agreed with the DAP's suggested amendments and additions to the "approved name" definition for all other chemicals. It was noted that including the name used in the SUSDP as the primary 'approved name' was particularly appropriate given that this was the name specifically considered and endorsed by the Committee.
- However, Members decided that these changes to the definition of "approved name" were broader than the scope of the review that was discussed in October 2008 and therefore should not be treated as editorial changes. As such the Members agreed to foreshadow these changes to allow for public comment on this issue.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matter under Section 52E(1) was (i) any other matters that the Committee considers necessary to protect public health.

Members noted that, despite an explicit foreshadowed decision regarding the proposed amendments to the definition for "approved name", no pre-meeting submissions had been received. Members remained generally supportive of the amendments agreed to at the October 2009 meeting.

One Member queried whether, with regard to human therapeutic use, there would be any problem using "approved for use by the Therapeutic Goods Administration" as there may be approved names for substances which did not have a registered or approved product. The Committee generally agreed, however, that "approved" related to the name and not the status of a product.

A Member also sought clarity as to whether the amendments were introducing a hierarchy for naming. Another Member confirmed that a hierarchy approach already existed and that the amendments under consideration largely clarified and updated the

existing definition. Other Members also asserted that, for products not regulated for the TGA or APVMA, the enforcement of approved name on labels would solely be a jurisdictional matter, and it was open to those authorities to determine how strictly they wished to apply the hierarchy.

A Member also asked under what circumstances, if the name in the SUSDP was an approved name, would there ever be need to refer to other names further down the hierarchy. Other Members noted that this would sometimes be necessary regarding compounds captured by group entries, or captured as salts / derivatives etc of scheduled substances.

RESOLUTION 2010/58 - 1

The Committee decided to amend the definition for "approved name" to include:

- reference to the TGA with regard to naming of poisons for human therapeutic use;
- reference to the APVMA with regard to naming of poisons for animal or agricultural use; and
- the amendments and updates as foreshadowed at the October 2009 meeting for scheduled ingredients in other products.

PART 1, INTERPRETATION – Amendment

"Approved name" – Amend entry to read:

"Approved name" means:

(a) in relation to a poison that is for human therapeutic use, the name approved for use by the Therapeutic Goods Administration;

(b) in relation to a poison that is for animal or agricultural use, the name approved for use by the Australian Pesticides and Veterinary Medicines Authority;

(c) in relation to all other poisons:

(i) the name used in an entry in these Schedules; or, if no such name is given,

(ii) the English name recommended by Standards Australia as the common name for the poison; or, if no such name is given,

(iii) the English name given to the poison by the International Organization for Standardization; or, if no such name is given,

(iv) the English name given to the poison by the British Standards Institution; or, if no such name is given,

(v) the name that would comply with the requirements of part (a) or (b) of this definition, or, if no such name is given,

(vi) the English name given to the poison by the European Committee for Standardization (CEN); or, if no such name is given,

(vii) the international non-proprietary name recommended for the poison by the World Health Organisation; or, if no such name is given,

(viii) the International Nomenclature Cosmetic Ingredient name for the poison listed in the International Cosmetic Ingredient Dictionary published by the Cosmetic Toiletries and Fragrance Association of America; or, if no such name is given,

(ix) the accepted scientific name or the name descriptive of the true nature and origin of the poison.

2.2 SUSDP, PART 2

No items.

2.3 SUSDP, PART 3

No items.

2.4 SUSDP, PART 5

No items.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

3. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCY(1)(c))

No items.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 CARBENDAZIM

PURPOSE

The Committee considered comments regarding the October 2009 carbendazim decision.

BACKGROUND

Carbendazim is a broad-spectrum benzimidazole fungicide. In addition to its agricultural applications, carbendazim is also used as a fungicide in paints, jointing compounds and sealants.

At the November 1982 meeting, the Committee agreed to reschedule benomyl from the exempt list (now Appendix B) to Schedule 6 due to developmental toxicity, genotoxicity and carcinogenicity concerns. Carbendazim is the primary metabolite and alleged mutagenic compound of benomyl. At the February 1983 meeting, the Committee decided to also reschedule carbendazim from the exempt list to Schedule 6.

At the February 1989 meeting, the Committee considered a request to exempt paints containing benomyl or carbendazim at 1 per cent or less. Members agreed that, while small amounts of fungicide for preservation of dried film should present no hazard, the exact manner of their use was needed in order to word the schedule entries correctly. At the August 1990 meeting, the Committee again considered fungicides in paints and agreed to an exemption cut-off for paints containing 0.5 per cent or less of carbendazim or benomyl.

At the June 2008 meeting, the Committee considered an extension of the 0.5 per cent exemption from the carbendazim Schedule 6 entry for paints to also include construction materials. A Member noted that, given the broad general use of paint, the exposure risk from use in construction materials, such as jointing compounds and sealants, was likely to be lower. The Committee agreed to broaden the exemption for paints to also include jointing compounds and sealants containing ≤ 0.5 per cent carbendazim.

At the October 2008 meeting, the Committee considered a review of benomyl prepared as part of the APVMA Chemical Review Program. This review:

- Recommended that benomyl be rescheduled to Schedule 7 as it was a developmental toxicant in laboratory animals in the absence of maternal toxicity and that the mechanism of action may be relevant to humans. The Committee agreed.
- Concluded that the hazard from applying paint containing 0.5 per cent benomyl was not significant, nor was any hazard anticipated from dried paint, given the low vapour pressure of benomyl and that it would be encapsulated within the paint film. The Committee decided to maintain the ≤ 0.5 per cent exemption for paint but did agree to also include benomyl in Appendix F Part 3 with Warning Statement 46 '*WARNING – Contains (name of substance) which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with (name of substance)*'.

At the October 2009 meeting, the Committee considered a review of carbendazim and thiophanate-methyl prepared by XXXXX as part of the APVMA Chemical Review Program. Carbendazim was nominated for review based on concerns over its potential to cause impairment of reproduction and development. This review recommended, and the Committee agreed, that carbendazim should be rescheduled to Schedule 7 as it was a developmental toxicant in laboratory animals in the absence of maternal toxicity and that the mechanism of toxicity may be relevant to humans.

The evaluator also advised that, from calculations based on published data, accidental oral ingestion of as little as 3.5 mg of carbendazim would be sufficient to reach the acute reference dose (ARfD) for testicular toxicity for an adult. At a concentration of 0.5 per cent in paint, the ARfD could be exceeded by accidentally swallowing 0.7 mL of the paint during the course of a days work. On this basis, Members concluded that an exemption for paints, jointing compounds or sealants containing 0.5 per cent or less of carbendazim was no longer appropriate.

DISCUSSION - SUBMISSIONS

In January 2010 XXXXX advised that it had only recently become aware of the October 2009 carbendazim decision. XXXXX vigorously objected to the October 2009 outcome, claiming that carbendazim was in nearly all exterior paints sold in Australia. XXXXX asserted that the impact of this decision on the Australian paint industry was such that a way must be found to change this situation.

Members were advised that, as no pre-meeting submissions were received for the October 2009 carbendazim consideration, no eligible further submissions were possible. Additionally, no comment at all was received in response to the carbendazim amendment before the cut-off for October 2009 further submissions. If a valid post-meeting submission had been received the Committee would have been obliged under sub-section 42ZCZ of the Regulations to reconsider the October 2009 decision.

XXXXX Application

Members were advised that XXXXX had submitted an application seeking the reintroduction of an exemption for paints, jointing compounds and sealants containing carbendazim. XXXXX proposed a new exemption cut-off of 0.1 per cent. This application was received prior to the deadline for applications to be considered at the June 2010 meeting.

Members also noted the following from the application:

Need for access

- Film biocides are used in paints, jointing compounds and sealants to provide fungicide protection to stop the growth of mould. The principle product used in Australia contains three actives, one of which is carbendazim. It was asserted that XXXXX use this product in their exterior paint formulations.
- It was asserted that there were no tested film biocide alternatives readily available for paint. To change the coatings formulation away from carbendazim, alternative film biocides would need to be identified, sourced and tested and this process would take a minimum of 2-3 years. The Australian Paint Authority Scheme testing alone required a two year testing period for exterior paints.
- Advised that the industry would move to a safer product if one could be found that meets the performance criteria and expectations. Ongoing research by XXXXX was still to identify a suitable alternative product to replace carbendazim.

Consequences of the October 2009 decision

- It was asserted that implementation of the new Schedule 7 entry, without exemptions, from 1 May 2010 would have catastrophic consequences for the manufacturers of paints, jointing compounds and sealants in Australia and the importers' of these products.
- The cost of the initial withdrawal of paint alone was asserted to be around XXXXX. It was also asserted that many local manufacturers' will be forced to cease operations, noting a paint industry annual turnover of ~$2.5 billion employing some 6,000 persons.
- It was asserted that without a usage level, exemption or moratorium, all affected stock would need to be withdrawn and destroyed.
- Also, the removal of all exterior coatings from the market would close down the exterior painting industry and the exterior construction industry. Few structures could be completed without suitable coatings.

Current use levels

- Paint manufacturers in Australia have voluntarily reduced carbendazim in their paint formulations, over time, to a current range of 0.03 to 0.12 per cent. Further, the

average amount is in the range 0.05 to 0.07 per cent, which represents close to 10 per cent of the previous limit or a 10 fold increase in safety over the current Standard.

Proposed new cut-off

- The European Union (EU) has reclassified carbendazim under the 29th Adaptation to Technical Progress (ATP) of the Dangerous Substances Directive. The main change to labelling was that products containing > 0.1 per cent were required to be labelled R46 – may cause heritable genetic damage. Products containing < 0.1 per cent required no special labelling.
- It was therefore recommended that scheduling harmonise with the EU reclassification of carbendazim i.e. products such as paints containing 0.1 per cent carbendazim or less to be sold without the need for special labelling requirements i.e. exempt from scheduling.
- Members also noted, that apart from the reference to the EU reclassification, the application did not provide any data or arguments as to why 0.1 per cent carbendazim would not pose a risk of testicular toxicity, the main concern considered at the October 2009 meeting.

XXXXX comment

XXXXX submitted a comment supporting XXXXX application. XXXXX advised that XXXXX also have specific interest with regard to sealants and jointing compounds. Members noted the following from XXXXX comment:

- Asserted that implementation of Schedule 7 for carbendazim without a cut-off would effectively remove sealant and jointing products from the market.
- Relevance of the October 2009 consideration for sealants and jointing compounds was not identified by XXXXX until January 2010. In this regard it was noted that the October pre-meeting Gazette specifically identified a proposal to amend the current scheduling of carbendazim from Schedule 6 to Schedule 7 and a review of the current exemption for paints containing 0.5 per cent or less of carbendazim. Asserted therefore that industry participants in the sealants and jointing products sector did not identify direct relevance of this notice to their situation.
- Advised that the retail sealant market (mould-resistant bathroom silicones and coloured gap fillers) was approximately XXXXX at the retail level, but was not yet able to ascertain whether all products contain carbendazim.
- Asserted that, given the nature of these products, their packaging and use, oral ingestion of any significant amounts of the formulated product appeared unlikely.
- XXXXX have advised that, whilst alternatives to carbendazim have, or are, being considered in product development, no tested products were currently available. Given the nature of the products, testing was undertaken over extended periods.

- Advised that carbendazim was included in sealant and jointing compound formulations at levels of less than 0.1 per cent. Supported XXXXX proposal for a cut-off from scheduling of 0.1 per cent or less in line with an EU cut-off.

Evaluator's comment

Further advice was sought from the evaluator with regard to the oral ingestion risk of carbendazim in light of the proposal for a 0.1 per cent cut-off. Members noted the following from the evaluator's advice:

- Regarding the oral ingestion risk from carbendazim in paints, the evaluator has calculated the likelihood of exceeding the ARfD by accidental oral ingestion.
- The ARfD for carbendazim is 0.05 mg/kg bw. For an adult (70 kg), this represents 3.5 mg of carbendazim (0.05 x 70 kg = 3.5 mg).
- At a concentration of 0.5 per cent the ARfD could be reached by accidentally swallowing 0.7 mL of product (3.5 mg / 5 mg/mL = 0.7 mL) during the course of a days work.
- At 0.1 per cent, this becomes an accidental swallow of 3.5 mL of product during a day.
- At 0.05 per cent, this becomes an accidental swallow of 7 mL of product during a day.
- At 0.01 per cent, this becomes an accidental swallow of 35 mL of product during a day.

The evaluator also reiterated the rationale for the setting of the ARfD for carbendazim. Members noted:

- The ARfD was currently set at 0.05 mg/kg bw.
- The basis of the ARfD was developmental and testicular toxicity.
- In two XXXXX gavage developmental toxicity studies, increased incidence of malformations affecting the head, spine and ribs were seen at doses of XXXXX and higher. These occurred in the absence of maternal toxicity and the NOEL for these effects was XXXXX.
- Testicular toxicity was observed in two separate XXXXX studies following a single XXXXX dose of XXXXX. Effects included premature release of immature germ cells 2 days post-exposure, atrophy of seminiferous tubules, decreased seminiferous tubule diameter, abnormal growth of efferent ductules and increased frequencies of micronuclei were observed in spermatids. In each case, this was the lowest dose tested.
- Since testicular toxicity can potentially arise following a single exposure, it was considered to be an appropriate toxicological endpoint to establish an ARfD.

- A 1000-fold safety factor, incorporating 10-fold each for intra and interspecies variation and an additional factor of 10, to account for the use of a LOEL, was used to establish the ARfD.

October 2009 discussion

Members also recalled the following from the October 2009 discussion:

- Carbendazim, at comparatively moderate doses, was a reproductive toxicant. It was a teratogen that could potentially cause severe and irreversible malformations in the foetus without concomitant maternal toxicity. It was therefore a developmental toxicant acting directly on the foetus during pregnancy. It was also demonstrated to act directly on the testes with a severity sufficient to impair testicular function. These effects on reproduction were demonstrated following administration of single doses of carbendazim.
- In relation to the existing exemption from scheduling of paints, jointing compounds and sealants containing 0.5 per cent or less of carbendazim, Members expressed concern about any person who accidentally swallowed as little as 0.7 mL of paint during the course of a days work. At a concentration of 0.5 per cent in paint, this was a consumption of 3.5 mg of carbendazim i.e. the ARfD.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits, (c) potential hazards, (d) extent and patterns of use and (e) dosage and formulation.

Members agreed that there appeared to be potential for significant regulatory impact from the October 2009 decision, noting that it was unfortunate that these industry concerns, and the alternative proposal, had not been raised during the public consultation for the October 2009 consideration.

A Member noted that the mode of action of carbendazim was well established and the observed toxic effects were consistent with this. As such, permanent impairment to testicular function was a serious risk. The Member argued that no data had been presented to dispute this concern and asserted that the Schedule 7 parent entry for carbendazim remained appropriate. The Member also asserted, and the Committee agreed, that the only question now to consider was whether this risk became sufficiently mitigated at low concentrations to justify an exemption cut-off.

The Committee then debated whether there were grounds for reintroducing a low concentration exemption for certain uses (paints, jointing materials and sealants), particularly noting new advice from the evaluator that at 0.1 per cent an ingestion of at least 3.5 mL was required to reach the ARfD (over the course of a day).

Several Members suggested that the risk of ingesting 3.5 mL of paint, jointing material or sealant was significantly less than the risk of ingesting 0.7 mL (the amount needed to reach the ARfD from a 0.5 per cent carbendazim preparation). One Member also asserted that the ARfD safety factor of 1000 may be too conservative, noting that the end point of concern, testicular toxicity, was only observed in a single species, with no adverse effects observed in any other species. The Member suggested that a safety factor of 100 may be more appropriate, noting that if this figure were used the ingestion volume would become an improbable 35 mL. Another Member argued that the safety factor was appropriately high because the ARfD was based on a LOEL rather than a NOEL as no clear end point could be established.

A Member also noted that the teratogenic effect was only observed when carbendazim was administered by gavage and suggested that this effect may well have resulted from a saturated metabolic pathway effect. Another Member agreed that there appeared to be a real concentration effect. Members therefore considered if there was potential for cumulative toxicity but noted that this appeared to be addressed for low concentrations as absorbed carbendazim was cleared within 72 hours, with no evidence of accumulation once absorbed.

A number of Members recalled that the European Union had set a cut off at 0.1 per cent carbendazim. Members additionally noted advice that worker dermal exposure modelling indicated that products containing 0.1 per cent carbendazim had acceptable exposure, whereas at 0.5 per cent gloves were required to mitigate the risks associated with dermal exposure. Members additionally noted that it appeared there was a real need for this material and that, at this time, no alternatives were available.

Members generally agreed, on the basis of the above points, that a cut-off of 0.1 per cent (for use in paints, jointing materials and sealants) appeared appropriate. However, Members noted that, in the absence of valid post-meeting comment from the October 2009 meeting, the Committee was unable to amend the October 2009 decision and was legislatively limited to foreshadowing this new exemption cut-off for consideration at the June 2010 meeting. Members agreed, however, that it was not reasonable to introduce new controls (no cut-off exemption) from 1 May 2010 (the standard implementation date for October 2009 decisions) when the Committee had already agreed to foreshadow overturning some of these controls in June 2010. Members additionally noted that it was not uncommon for decisions to have delayed implementation dates.

Members therefore agreed to delay the implementation of the October 2009 decision to 1 January 2011. Members additionally noted that, should the June 2010 decision differ from the October 2009 meeting (as had been foreshadowed) then this subsequent decision would replace the October 2009 decision.

RESOLUTION 2010/58 - 2

The Committee decided to delay the implementation of the October 2009 carbendazim decision to 1 January 2011. The Committee also decided to foreshadow an exemption

from the requirements of scheduling for paints, jointing compounds and sealants containing 0.1 per cent or less for carbendazim.

Schedule 7 – Amendment (foreshadowed decision for the June 2010 meeting)

CARBENDAZIM – Amend entry to read:

CARBENDAZIM **except** in paints, jointing compounds and sealants containing 0.1 per cent or less for carbendazim.

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

5.1 SUSDP, PART 4

5.1.1 LYE WATER – ALKALINE SALTS, POTASSIUM HYDROXIDE AND SODIUM HYDROXIDE

PURPOSE

The Committee considered the scheduling of the various actives in lye water – alkaline salts, potassium hydroxide and sodium hydroxide.

BACKGROUND

Lye water can refer to either sodium hydroxide, potassium hydroxide or a mixture of both in aqueous solution. Lye water can also refer to sodium or potassium carbonate solutions. It is used in the traditional manufacture of soap and as a cleaning agent. Lye water is also an ingredient in Asian cooking where it is usually added in small amounts (tablespoon volumes) to bind ingredients such as rice.

At the June 2005 meeting, the Committee was informed of an analysis of a cooking condiment marketed as "Lye Water" following the hospitalisation of a child with severe burns to the oesophagus and stomach. The product had a pH of approximately 14.

At the February 2006 meeting, the Committee was informed about three incidents of poisoning occurring from ingestion of lye water (the products were used as an ingredient in Asian cooking). The Committee particularly noted concerns surrounding the packaging of lye water products and the ease with which they can be accessed by infants and children. The Committee agreed that a critical step in controlling the lye water risk was to mandate Child Resistant Closures (CRC) for lye water containers. The Committee agreed to foreshadow that food additives captured by the alkaline salts entries were to be required to have a CRC. The Committee noted that the action foreshadowed together with the existing CRC requirements for sodium and potassium hydroxide, would achieve the following:

- where sodium or potassium hydroxide were part of a lye water formulation the product, where the volume was 2.5 litres or less, was required to be fitted with a CRC, regardless of the pH of the product; and
- where lye water, for food additive use, had been made from alkaline salts such as sodium or potassium carbonate, with no sodium or potassium hydroxide, then the product, where the volume was 2.5 litres or less, would also now be required to be fitted with a CRC, if the pH was > 11.5.

At the June 2006 meeting, the Committee agreed to the foreshadowed decision and amended Part 2, Paragraph 25(1) to require that food additives captured by the alkaline salts entries (i.e. lye water with a pH > 11.5) were to have a CRC where the volume was 2.5 litres or less.

At the June 2007 meeting, the Committee was informed that XXXXX had retrieved approximately 60 bottles of lye water from small local supermarkets. Testing revealed a pH of approximately 14. The bottles did not have the required CRC's. Three distributors were identified from the bottles, all in NSW. XXXXX was notified and had spoken with the distributors to resolve this issue.

DISCUSSION - SUBMISSIONS

Application

XXXXX requested a prohibition on the availability of lye water liquid preparations packed and labelled as a food additive for domestic use, with a pH of more than 11.5, through a new entry for 'ALKALINE SALTS' in Appendix C. Products for commercial use were not intended to be addressed by the application. The applicant requested that the new Appendix C entry read 'The hydroxide, carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination in liquid preparations when packed and labelled as a food additive the pH of which is more than 11.5'.

Members also noted the following from the application:

- The submission had been prepared in collaboration with paediatric specialist health professionals, poisons information centres, injury prevention and surveillance units and health departments in XXXXX.
- These products presented a unique poisoning risk, particularly as a result of accidental ingestion by children. Factors contributing to this unique risk included:
  - The availability of lye water with an extremely alkaline pH (products had been measured up to ~ pH 14). Ingestion of even small amounts of these products could cause severe acute caustic injuries that could be life threatening and result in adverse chronic sequelae.

- Daily use as a food additive in home cooking can predispose to storage within easy reach of children, and decanting or incomplete closure of CRC to increase ease of use.
- General public perception that food additives were safe for ingestion which, combined with routine observation by children of lye water added to food, contributed to a conflict with traditional poisoning prevention messages that were used for other household chemicals of sufficient risk to require a CRC (e.g. keep out of the reach of children).
- Use in communities with a poor knowledge of the toxicity of the product available in Australia, variable literacy and English-speaking skills, and familiarity with a similar and less caustic product that was not readily available in Australia.
- Post hoc labelling of imported products with minimal warning directions and poor label clarity.

- CRC as the current primary poisoning prevention measure (in conjunction with public education) were failing to mitigate this risk, which was being disproportionately borne by children in the African-Australian community.
- Evidence had been provided by means of five case study reports, 21 tabulated national exposures to lye water from Poisons Information Centres and hospital data since 2005 and a literature review of caustic ingestion injuries:
  - to substantiate the severity of injury, complications and overall morbidity following the ingestion of lye water products in Australia; and
  - to support that access, ingestion and injuries in Australian children had continued to occur, with 9 paediatric accidental ingestions of lye water products reported to national Poisons Information Centres since the requirement for CRC came into effect in January 2007.
- Potentially less toxic lye water products with a pH below 11.5 were available in Australia, indicating that extreme pH was not required for efficacy of the product.
- Restricting the availability of lye water products in Australia to those with a pH below 11.5 would effectively protect public health by minimising the risk of harm from accidental or intentional ingestion, while sustaining traditional cooking methods and cultural diversity by providing less toxic products that remain fit for intended purpose. A pH below11.5 reduced the potential for severe and life-threatening injury, cumulative morbidity (e.g. physical, psychological and socio-economic consequences of caustic ingestion injury and required treatment) and the long-term risk of gastrointestinal dysfunction and malignancy.

The applicant also addressed some additional matters specifically against 52E. Members particularly noted the following:

(a) Toxicity and safety

- Alkaline solutions with a pH of 12 and above had been reported to cause caustic burns and injuries to human oesophageal and gastric epithelium as a result of liquefaction necrosis. Increasing severity of injury was dependent upon pH, duration of mucosal exposure, the buffering capacity of the agent, concentration, physical state, presence of food in stomach and volume of exposure.
- The innocuous taste and odour of alkaline products may contribute to the ingestion of larger quantities.
- Oesophageal ulceration with liquefaction necrosis had also been observed in animal tissue models at pH of 11.5 and above. Alkali ingestions had been reported to cause burns at all levels of the digestive tract from the oral cavity to the proximal duodenum.
- Presenting symptoms include drooling, coughing, retrosternal and epigastric pain, refusal of oral intake, lip swelling, tongue erythema, dyspnoea, oral ulceration and vomiting (which could increase the duration of mucosal exposure in the oesophagus and increase severity of injury).
- The extreme alkalinity of lye water products also predisposes to risk of dermal and eye injury.
- The management of paediatric alkaline exposures had inherent risks that contribute to acute morbidity that were associated with diagnostic procedures (e.g. potential for iatrogenic perforation with endoscopy) and treatments (e.g. corticosteroids).
- The nature of these burns predisposes to multiple complications; the most likely being fibrotic scarring that could result in oesophageal stricture formation requiring dilatation or surgical intervention.
- There was a reported association between the ingestion of lye products (e.g. sodium hydroxide and/or potassium hydroxide-containing cleaning products) and an increase in the development of oesophageal carcinoma (ranging from 2-30 per cent).
- The incidence of accidental lye water ingestions by children was considered relatively low; however, the incidence of serious cumulative morbidity was high and potentially long term or even fatal.
- Paediatric lye water ingestions and injuries continue to occur in Australia since the mandating of CRCs.
- Clinical evidence describing the severity of injury in children following the ingestion of Australian lye water products had been provided.
- Extensive supporting evidence existed in the literature for the severity of acute injury and potentially life-threatening complications following the ingestion of alkaline solutions with similar toxicological profiles as Australian lye water products.

(b) Risks and benefits

- There was a risk of accidental or intentional ingestion of this extremely alkali food additive which was associated with the potential for severe acute injury with adverse long-term sequelae following small ingestions.
- Lye water products were safe to ingest when used for their intended purpose i.e. once incorporated in food where small amounts were diluted during the cooking process. Lye water was used in various Asian and African communities as a food additive in cooking to add flavour or soften foods such as corn, beans, maize, okra, meat, rice and noodles. Lye water could also be used to make soap and for other cleaning purposes.

(c) Potential hazards

- Daily use of lye water as a food additive in home cooking presents a unique health hazard which is failing to be mitigated by the exposure-prevention strategy currently in place - CRC.
- Frequent use encourages incomplete closure or deterioration then failure of CRCs; encourages decanting (e.g. to avoid 'ease of opening' issues with CRCs); leads to products being routinely stored within easy reach of children (e.g. on a kitchen bench or in a refrigerator); and results in children witnessing the everyday addition of lye water to their food.
- These behaviours, in addition to difficulties in promoting poisoning prevention for food additives (which were generally considered by the public to be safe to ingest), predispose to the accidental ingestion of lye water by children and the associated risk of severe injury.

(d) Patterns of use

- Lye water was used as a food additive, predominantly in Asian and African cooking.
- Lye water products had a similar purpose (although are much more toxic due to higher pH) to solid salt products commonly used in Africa (e.g. Magadi soda which was not readily available in Australia).

(e) Dosage and formulation of lye water products

- Small amounts (spoonfuls) of lye water were added to food for softening and flavouring purposes. Accidental and intentional ingestions range in volume.
- Lye water food additive products contain alkaline salts in aqueous solution with varying compositions of sodium or potassium hydroxide or sodium or potassium carbonate or mixtures of any of these salts. For example, one product available in Australia contained 48.8 per cent (w/w) potassium carbonate and 2.5 per cent (w/w) sodium carbonate with an alkalinity equivalent to ~ 47 per cent w/v) sodium hydroxide.
- There was no evidence of any lye water products manufactured in Australia.

(f) Need for access to lye water

- The submission argued that access to lye water products promotes and protects Australia's cultural diversity, but other substances such as bicarbonate of soda and soda ash (sodium carbonate) had similar effects on food as lye water with a lower pH and toxicity.
- Some lye water products imported into Australia had been identified with a lower pH, in the order of 11.4, suggesting that products were available on the market that were likely to be effective with a lower toxicity and lower potential for severe injury.

Pre-meeting submissions

Members noted that no pre-meeting submissions were received.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (c) potential hazards, (d) extent and patterns of use and (f) the need for access to a substance.

A Member noted that there were no pre-meeting comments and queried whether this may mean that potentially affected companies might not have been aware of this consideration, as they would likely be small speciality manufactures rather than large companies. A Member advised, however, that in fact there appeared to be only one lye water preparation manufactured in Australia, noting that this product was currently marketed for commercial use only. Members generally agreed that the lye water consideration had been appropriately published as per the usual practice and legislative requirements and it was not necessary to delay this consideration.

The Committee discussed the inherent properties of lye water and its poisoning risk – particularly consequences of accidental ingestion by children. It was noted that the lye water accidental poisoning issue was considered at previous meetings and at that time the Committee had decided that the risks from lye water with a pH of more than 11.5 were adequately addressed through a CRC requirement (along with public education and labelling). Several Members asserted that the information now before the Committee was sufficient to establish that this existing level of control had not been sufficient, noting lye water accidental ingestions and injuries had continued to occur since the mandating of CRCs.

Members generally agreed that, for those lye water preparations with a pH of more than 11.5, the extremely alkaline nature, even in small amounts, could cause life threatening caustic injuries. A Member noted, however, that the risk of ingestion was most significant with regard to use in the domestic setting. The Member argued that there appeared to be scope for continuing to allow non-domestic access (such as restaurants or industrial food processing) to high strength lye water products. Another Member noted that there appeared to be alternative preparations available with pH of 11.5 or less which

should be sufficient for domestic use. The Committee therefore agreed to restrict the domestic availability of lye water by capturing domestic food additive preparations, with pH of more than 11.5, through specific entries to this effect for alkaline salts, sodium hydroxide and potassium hydroxide in Appendix C.

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The Committee decided to include alkaline salts, sodium hydroxide and potassium hydroxide in liquid or semi-solid food additive preparations for domestic use, the pH of which is more than 11.5, in Appendix C.

Schedule 5 - Amendments

ALKALINE SALTS – Amend entry to read:

† ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination:

(a) in solid orthodontic device cleaning preparations, the pH of which as an "in-use" aqueous solution is more than 11.5;

(b) in solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solutions or mixture is more than 11.5 but less than or equal to 12.5;

(c) in other solid preparations, the pH of which in a 10 g/L aqueous solution is more than 11.5; or

(d) in liquid or semi-solid preparations the pH of which is more than 11.5, unless:

(i) in food additive preparations for domestic use; or

(ii) in automatic dish washing preparations for domestic use with a pH of more than 12.5,

except when separately specified in these Schedules.

POTASSIUM HYDROXIDE – Amend entry to read:

† POTASSIUM HYDROXIDE (excluding its salts and derivatives) in preparations containing 5 per cent or less of potassium hydroxide being:

(a) solid preparations the pH of which in a 10 g/L aqueous solution is more than 11.5; or

(b) liquid or semi-solid preparations, the pH of which is more than 11.5 **except** in food additive preparations for domestic use.

SODIUM HYDROXIDE – Amend entry to read:

† SODIUM HYDROXIDE (excluding its salts and derivatives) in preparations containing 5 per cent or less of sodium hydroxide being:

(a) solid preparations the pH of which in a 10 g/L aqueous solution is more than 11.5; or

(b) liquid or semi-solid preparations, the pH of which is more than 11.5 **except** in food additive preparations for domestic use.

Schedule 6 – Amendments

SODIUM HYDROXIDE – Amend entry to read:

† SODIUM HYDROXIDE (excluding its salts and derivatives) **except**:

(a) when included in Schedule 5;

(b) preparations containing 5 per cent or less of sodium hydroxide being:

(i) solid preparations the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

(ii) liquid or semi-solid preparations the pH which is 11.5 or less, or

(c) liquid or semi-solid food additive preparations, the pH of which is more than 11.5, for domestic use.

POTASSIUM HYDROXIDE – Amend entry to read:

† POTASSIUM HYDROXIDE (excluding its salts and derivatives) **except**:

(a) when included in Schedule 5;

(b) preparations containing 5 per cent or less of potassium hydroxide being:

(i) solid preparations the pH of which in a 10 g/L aqueous solution is 11.5 or less; or

(ii) liquid or semi-solid preparations the pH of which is 11.5 or less, or

(c) in liquid or semi-solid food additive preparations, the pH of which is more than 11.5, for domestic use.

APPENDIX C – Amendment

ALKALINE SALTS – Amend entry to read:

ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium, alone or in any combination for domestic use:

(a) in liquid or semi-solid food additive preparations, the pH of which is more than 11.5;

(b) in solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solutions or mixture is more than 12.5; or

(c) in liquid or semi-solid automatic dishwashing preparations the pH of which is more than 12.5.

APPENDIX C – New Entries

POTASSIUM HYDROXIDE (excluding its salts and derivatives), in liquid or semi-solid food additive preparations, for domestic use, the pH of which is more than 11.5.

SODIUM HYDROXIDE (excluding its salts and derivatives), in liquid or semi-solid food additive preparations, for domestic use, the pH of which is more than 11.5.

5.1.2 NATAMYCIN

PURPOSE

The Committee considered the scheduling of natamycin.

BACKGROUND

Natamycin (pimaricin) is a polyene macrolide antibiotic and antifungal produced by submerged aerobic fermentation of *Streptomyces natalensis* and related species. The activity of natamycin against yeasts and moulds, but not bacteria, makes it convenient for use in foods that undergo a ripening period after processing. Its low solubility in water and most organic solvents also makes it suitable for the surface treatment of foods. Natamycin is used topically in veterinary medicine to treat mycotic infections, such as ringworm in cattle and horses. Previously, it was used topically against fungal infections of the skin and mucous membranes in humans. Its medical use is now confined to topical

treatment of corneal fungal infections and the prevention of such infections in users of contact lens.

A search of the Committee records failed to locate any information regarding when natamycin was first scheduled and the reasons for the current Schedule 4 listing of natamycin.

At the August 1983 meeting, the Committee noted that the Australian Drugs and Evaluation Committee (ADEC) considered and approved an application for the use of natamycin as a fungicide on cheese and cured manufactured meat surfaces. The Committee therefore agreed to amend the Schedule 4 natamycin entry to exclude use as a permitted food additive.

At the November 1984 meeting, the Committee noted that the presence of scheduled substances in food, either due to the addition of permitted additives or the presence of pesticides residues, meant that the foodstuff would be scheduled. The Committee agreed that this anomaly could be rectified by the addition of a general exemption (now the Appendix A food exemption) and consequently amended the natamycin Schedule 4 entry by removing 'where used as a permitted food additive'. Therefore, natamycin incorporated into a food would qualify for the Appendix A general exemption. However, prior to incorporation into food the natamycin additive would appear to be Schedule 4.

Currently, both cassia oil and cinnamon bark oil are listed in Schedule 5, with exemptions from scheduling when used as food additives. Nisin and thaumatin are included in Appendix B with an 'area of use' tag of 3.2 (food additive).

DISCUSSION - SUBMISSIONS

XXXXX proposed that the Schedule 4 natamycin entry be amended to exempt natamycin when supplied, packed and labelled for use as a food additive (as authorised by Food Standards Australia New Zealand (FSANZ)). XXXXX identified several reasons for exempting natamycin when used as food additive:

- Natamycin has low soluble in water and therefore has negligible absorption when taken orally.
- It had very low toxicity.
- TGA had approved it as an active ingredient. Members noted, however, that there was no TGA approved product currently available.
- It was used in the food industry to prevent fungal growth on food products. It was approved as a food additive (#235) by FSANZ for use on cheese, cheese products and fermented uncooked comminuted meat products.
- Prior to adopting the current Schedule 4 wording in 1990 the NSW entry read 'Natamycin **except** when used as or packed for use as a food additive'.

- Nisin, apparently the only other antibiotic approved as a food additive, is in Appendix B. Nisin had not been used in human medicine.
- As an approved food additive, a number of food manufactures were using natamycin. However, natamycin when captured by Schedule 4 appears to require a licence or authority to 'obtain and use a Schedule 4 medicine'. This anomaly was brought to light by a wholesale supplier who queried the legality of supplying natamycin to food manufactures who do not hold such a licence or authority.

Pre-meeting submission

XXXXX supported the proposal that natamycin be exempt from scheduling when used as a food additive. The submission further advised that natamycin is included in Schedule 1 of Standard 1.3.1 – Food Additives (of the *Australia New Zealand Food Standards Code;* the Code). As a food additive it was permitted to be added to a limited range of foods in Australia and New Zealand. As per the Standard 1.3.1, natamycin may only be added to the surface of cheese (rind) and uncooked fermented manufactured meat at specified levels.

Application to the June 2010 meeting

Members noted that XXXXX had submitted a valid scheduling application for the June 2010 meeting. The application had not been evaluated, but Members noted the following:

- Natamycin was permitted to be used as a food additive by FSANZ and was listed in the Schedule to Standard 1.2.4 and Schedule 1 to Standard 1.3.1 of the Code. This indicated that FSANZ had reviewed all the available relevant scientific literature and decided that the use of natamycin in two categories of product (surface of cheese and uncooked fermented manufactured meat) was safe for human consumption when used as directed by Schedule 1 of Standard 1.3.1.
- The applicant requested that natamycin, when used as a food additive, should be exempt from scheduling. This will facilitate the possession, sale and supply of natamycin for uses as a food additive consistent with approval granted by FSANZ and the Code.

Toxicity and safety

- Natamycin has a long history of safe use in foods and was approved by regulatory authorities in more than 70 countries, including the United States and the European Union, as a food additive to control the growth of yeasts and moulds. In South Africa, natamycin was permitted for use in a range of products, including yoghurts, fish products, wine and fruit juices. In the United States, natamycin was permitted to be used in cheese, non-standardised salad dressing and soft tortillas.
- The FAO/WHO Joint Expert Committee on Food Additives (JECFA) reviewed the safety of natamycin and assigned an acceptable daily intake (ADI) of 0.3 mg/kg bw/d (http://www.inchem.org/documents/jecfa/jecmono/v48je06.htm).

- Recently, the European Food Safety Authority (EFSA) noted limitations, such as animal study design, limited number of animals, lack of a carcinogenic study and inadequate human data, in the present safety database and concluded that an ADI could not be established. However, EFSA noted that the information on the metabolism suggested that it was not absorbed in any significant extent in the gastrointestinal tract and was rapidly excreted in faeces either unchanged or as degraded products.
- In 2004, responding to the FSANZ initial assessment report pertaining to an application to extend the use of natamycin into additional foods, the Department of Human Services, Victoria and the National Health and Medical Research Council (NHMRC) Expert Advisory Group on Antimicrobial Resistance (EAGAR) raised concerns over the possible development of antimicrobial resistance in humans resulting from a further extension of use of natamycin in foods. However, neither advocated banning the current use of natamycin as a food additive.

Risks and benefits

- There were no known risks associated with the use of natamycin when it was used as a food additive in accordance with Schedule 1 of Standard 1.3.1 of the Code.
- As mentioned earlier, JECFA raised concerns over the possible development of antimicrobial resistance in humans relating from a further extension of use of natamycin in foods. JECFA, however, in their 2002 re-evaluation of natamycin noted that "Although use of natamycin as an antifungal agent in food may result in exposure of the endogenous flora to trace quantities of antimicrobial residues, bacteria in the human gastrointestinal tract are not affected by polyenes, and the Committee concluded that disruption of the colonization barrier is not a concern. Fungi are found in much smaller amounts than bacteria in the human gastrointestinal tract, and the negative results in studies of acquired resistance indicate that selection of natamycin-resistant fungi is not an issue."
- The EFSA in their December 2009 decision indicated that there was no concern for the induction of antimicrobial resistance.
- Although fungicidal activity of natamycin is dose-related, key benefits of using this as a food additive include:
  - Improving food safety by protecting treated foods against mycotoxin production such as aflatoxins; and
  - Self life extension or maintenance by controlling and delaying fungal and yeast growth.

Potential hazards

- None known when used in accordance with Schedule 1 of Standard 1.3.1 of the Code.

XXXXX.

Additional points from the JECFA review

Members also noted the following from the JECFA 2001 World Health Organisation (WHO) Food Additives Series report on natamycin:

Short-term toxicity

- Oral administration of natamycin at doses of 50 to 70 mg/kg bw per day for 5 to 10 weeks had no effect on the growth, blood or tissue of rats. However, a daily oral dose of 150 mg/kg bw for 9 weeks caused some growth inhibition, and a daily dose of 500 mg/kg bw caused 30 per cent of the rats die with in two weeks.
- Groups of beagle dogs received diets containing natamycin at a concentration of 0, 125, 250 or 500 mg/kg for two years. All but one dog that receiving 250 mg/kg survived for two years, the death was unrelated to exposure to natamycin. No effects were seen on food intake, but males receiving the highest concentration did not grow as rapidly as controls initially, and after 15 months, when the dietary intake was reduced, some animals were unable to maintain a satisfactory body weight. The results of haematological and clinical chemical studies revealed no abnormalities. No effects of significance were found on organ weights and gross and microscopic examination showed no pathological changes.

Long term study and carcinogenicity

- Groups of rats received diets containing natamycin at a concentration of 0, 125, 250, 500 or 1000 mg/kg for two years. The animals remained in good health, and their survival was unaffected by treatment. Inhibition of growth rate and diminished food intake were seen only for animals of each sex receiving the highest concentration. The results of haematological investigations and determination of organ weights and gross and microscopic lesions showed no differences between treated and control groups. The numbers and types of tumours found in natamycin-treated rats were not significantly different from those in untreated animals.

Genotoxicity

- *In vitro* studies conducted with natamycin at a concentration of 1 per cent and its known degradation products (aponatamycin, dinatamycinolidediol, and mycosamine) at 0.5 per cent and at pH and nitrite conditions similar to those in preserved food products such as cheese and sausages, were reported to have no mutagenic activity in *Bacillus subtilis* under the conditions tested. However, the report indicated that no actual data were presented to verify this statement.
- An *in vivo* study found no differences between control and test animals in respect of the numbers of implantation sites or live or dead foetus or the mutagenic index.

Reproductive toxicity

- A multigeneration study involving rats receiving diets containing natamycin at a concentration of 0 or 1000 mg/kg found the pups of natamycin treated animals had lower mean body weights at weaning than control pups. However, examination of the

results showed that their fertility, gestation, lactation and viability indices were similar to or better than those of the controls. There was a low incidence of abnormalities among pups in this study, but none could be attributed to treatment.

Developmental toxicity

- Female rats from the second litters of a F1 generation from a three-generation reproductive toxicity study were mated with untreated males. The females were given the same dose of natamycin as their parents (0, 5, 15, 50 or 100 mg/kg bw/day) during the 6 to 15 days of gestation and were killed and examined on day 20. No differences were found between control and test animals in respect of the numbers of pregnancies, live litters, implantation sites, resorption sites, live and dead foetus, or skeletal and soft tissue abnormalities.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (c) potential hazards, (d) extent and patterns of use and (f) need for access.

The Committee discussed the current use patterns of natamycin in Australia. A Member noted that natamycin was an antifungal / antibiotic that was not currently used in Australia for human therapeutic use but was being used in other countries as a topical antibiotic. Another Member, however, asserted that natamycin, although not registered as an antibiotic, was being used for certain purposes (mainly as eye drops) in Australian hospitals. The Member further commented that to date there had been no evidence resistance developing following natamycin treatment.

Several Members noted that natamycin had low toxicity and low oral bioavailability and asserted that natamycin when used as a food additive should be exempt from scheduling. These Members additionally highlighted the following from the tabled information which supported such an application:

- FSANZ had approved natamycin to be used on / in certain foods;
- natamycin had been approved in several other countries, including the United States and the European Union, and was being used in / on a range of foods;
- natamycin already in food would be exempt due to the Appendix A food entry and there was no reason to treat the food additive product, before incorporation into food, any differently; and
- reiterated the point from the 2002 JECFA report that “fungi are found in much smaller amounts than bacteria in the human gastrointestinal tract, and the negative results in studies of acquired resistance indicate that selection of natamycin-resistant fungi is not an issue”.

The Committee therefore agreed that use of natamycin as a food additive was sufficiently controlled by FSANZ requirements and did not require additional scheduling controls.

Members also noted that as FSANZ separately stipulates controls as to whether a natamycin preparation would qualify as a permitted food additive, it would not be necessary to reproduce this in scheduling through an active reference to FSANZ.

Members also noted that 'when used as a food additive' would not exempt the wholesalers who supply natamycin to someone else to use as a food additive. Members therefore agreed that the entry should read 'for use as a food additive'.

Other issue

A Member highlighted that natamycin was also known as pimaricin. Members agreed to include a new cross-reference in the SUSDP index for clarity.

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The Committee decided to exempt natamycin from the requirements of scheduling for use as a food additive.

Schedule 4 – Amendment

NATAMYCIN – Amend entry to read:

NATAMYCIN **except** for use as a food additive.

5.2 SUSDP, PART 5

No items.

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

6.1 DELTAMETHRIN

PURPOSE

The Committee considered the scheduling of deltamethrin.

BACKGROUND

Deltamethrin is a non-composite synthetic dibrom-cyanopyrethroid insecticide, containing only the d-cis-isomer. It is a broad spectrum, non-cumulative insecticide and a neurotoxic agent with good contact and stomach action. Deltamethrin is non-systemic in plants.

Deltamethrin, a fourth generation pyrethroid, is highly resistance to exposure to sunlight and air. Because it is stable in the environment, deltamethrin may be carried by water or air to areas where the compound may endanger non-target species such as birds, reptiles,

fish and plankton. Deltamethrin products are registered for use in Australia, and many other countries. However, Denmark has banned the outdoor use of deltamethrin products, due to concerns for the safety of the environment.

At the February 1979 meeting, the Committee listed decamethrin (also known as deltamethrin) in Schedule 6. At the May 1979 meeting, the Committee agreed to list decamethrin in Schedule 7.

At the November 1988 meeting, the Committee considered the scheduling of an aqueous suspension formulation and agreed to a Schedule 5 entry for 1 per cent deltamethrin when formulated with no organic solvent other than a glycol. At the February 1993 meeting, the Committee considered the scheduling of a 2.5 per cent deltamethrin formulation and agreed that this should be captured in Schedule 6.

At the February 2002 meeting, the Committee considered the scheduling of a 25 per cent deltamethrin insecticide. The Committee agreed that, although the acute toxicity profile of the product was appropriate for Schedule 5, Members remained concerned of the potential for neurotoxicity and the likely flow-on effects for other deltamethrin products. Accordingly, the Committee agreed that preparations containing 25 per cent or less should be listed in Schedule 6.

At the October 2004 meeting, the Committee agreed to reschedule 25 per cent deltamethrin when formulated as water dispersible granules, from Schedule 6 to Schedule 5. At the June 2008 meeting, the Committee decided to expand the Schedule 5 deltamethrin listing for aqueous preparations (when no organic solvent other than a glycol is present) from 1 per cent to 5 per cent.

DISCUSSION - SUBMISSIONS

XXXXX had prepared an evaluation report on an application to APVMA by XXXXX to register a new XXXXX product, XXXXX, containing deltamethrin at XXXXX. The evaluator had made the following recommendations:

XXXXX

Public Health Standards

- The ADI for deltamethrin was established in 1980 at 0.01 mg/kg bw/day, based on a NOEL of 1 mg/kg bw/day in a chronic XXXXX study and using a 100-fold safety factor.
- No ARfD had been established for deltamethrin.
- Deltamethrin is currently in Schedule 7. There are cut-offs to Schedule 6 and Schedule 5, including one to Schedule 5 for deltamethrin 'in other preparations containing 0.5 per cent or less of deltamethrin'. Based on the toxicology profile of XXXXX, a classification of Schedule 5 was considered appropriate.

- The applicant, however, had requested a review of this scheduling status, stating that the toxicological profile of XXXXX would suit an unscheduled product. Given that the product had only a slight risk of eye irritation, with reversibility within XXXXX hours and no corneal effects, it may be appropriate to include preparations containing 0.05 per cent or less of deltamethrin in Appendix B. Members recalled that the usual practice would be to create an exemption from scheduling cut-off rather than an Appendix B listing.

XXXXX

Technical Grade Active Constituent

Members noted that no new acute toxicity studies were submitted. The applicant had instead referred to previously assessed deltamethrin applications.

Members also noted the following from the evaluation report regarding the toxicity of the deltamethrin technical grade active constituent (TGAC) from prior assessments:

Dermal absorption

- The dermal absorption of deltamethrin is in the order of 3 to 4 per cent of the applied dose. An *in vitro* study comparing XXXXX skin to human skin sections found that XXXXX skin absorbed much more of a liquid deltamethrin preparation than human skin.

Acute toxicity

- Deltamethrin has moderately high acute toxicity, with XXXXX. Deltamethrin is not an irritant on XXXXX skin and only a mild eye irritant in XXXXX. It does not cause sensitisation in XXXXX.

Repeated dose

- Subchronic studies performed in XXXXX resulted in decrease in male body weight at doses of XXXXX, with no pathological changes. Studies in XXXXX, at doses up to XXXXX for XXXXX weeks, resulted in decreases in weight gain and the occurrence of liquid faeces in all treatment groups. Depression of the patellar reflex was observed at XXXXX.
- In a 3-generation reproduction study in XXXXX, there were no clinical signs of toxicity in the parents although there was a decrease in bodyweight at the high dose level. XXXXX body weight was somewhat lower at the high dose level.

Teratology

- In two studies in XXXXX, maternal toxicity was observed particularly at the higher dose level. There was a significant increase in the number of supernumerary ribs. In XXXXX, at doses of XXXXX and above, there was a dose-related decrease in maternal bodyweight gain. Delayed ossification was seen at XXXXX. XXXXX, at

doses up to XXXXX, there was a slight reduction in maternal bodyweight gain at the high dose level and also a decrease in foetal bodyweight at this dose level.

Chronic toxicity

- Chronic studies performed in XXXXX showed no effect on behaviour, body weight, or on biochemical, haematological or urinanalytical parameters. There was no increase in tumour incidence. Histopathological was unremarkable. In XXXXX, there was no change in behaviour, and a small decrease in bodyweight gain at the high dose level. There was no significant change in biochemical or haematological parameters. There was increase in intestinal adenomas in the tests of high dose males.
- Genotoxicity tests indicated that no increase in chromosome aberrations or sister-chromatid exchange (SCE) in XXXXX.
- In a neurotoxicity study in XXXXX, deltamethrin at a single dose up to XXXXX induced no clinical, macroscopic or histological signs of delayed neurotoxicity.

Human adverse effect reports

- The evaluator advised that clinical observations of production workers and agricultural workers have indicated that deltamethrin is irritating to skin and mucous membranes. Initial lesions were tenacious and painful pruritus (prickling sensation), followed by a blotchy burning sensation with blotchy erythema. Effects lasted for several days.

Members noted the recommended hazard classification for deltamethrin from the evaluation report. Deltamethrin is listed on the Australian Safety and Compensation Council (ASCC) Hazardous Substances Information System (HSIS) Database (ASCC, 2005) with the following phrases:

Conc.≥25 per cent

- Toxic by inhalation and if swallowed.

3 per cent < Conc. < 25 per cent

- Harmful by inhalation and if swallowed.

Formulated product

XXXXX toxicology studies on the XXXXX deltamethrin product were submitted. The evaluator concluded that the acute toxicology studies had been conducted in accordance with contemporary test guidelines and were considered to be adequate for the assessment.

Members noted the following summary of the product's toxicity data from the evaluation report:

XXXXX

- The product was considered to have low acute oral (XXXXX) and dermal (XXXXX) toxicity. A XXXXX hour inhalation study in XXXXX indicated that the product had low inhalational toxicity (XXXXX). The product was neither a skin irritant nor a skin sensitiser.
- The product was, however, found to be a slight eye irritant.

XXXXX

Pre-meeting submissions

XXXXX had recommended a cut-off from scheduling for products containing 0.06 per cent deltamethrin. The submission also argued that the World Health Organisation (WHO) classifies deltamethrin as a Class II (moderately hazardous) pesticide and assigns an LD_{50} of 135 mg/kg. It was asserted that an extrapolation from this LD_{50} value would mean that a product with 2.7 per cent or less deltamethrin will have an LD_{50} of 5000. The applicant therefore asserted that products with 0.06 per cent deltamethrin can be exempt from scheduling.

XXXXX supported exempting preparations containing 0.05 per cent or less of deltamethrin from scheduling. The submission further asserted that products containing 0.05 to 0.07 per cent deltamethrins are available on the Australian market. XXXXX therefore requested that products containing 0.1 per cent or less of deltamethrin be exempt from scheduling.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety and (c) potential hazards.

The Committee generally agreed that, except for slight eye irritancy, 0.05 per cent deltamethrin had low acute oral, dermal and inhalation toxicity. A Member noted that the eye irritancy was minor, and asserted that the overall weight of evidence would justify exempting this concentration of deltamethrin from scheduling.

A Member queried, however, whether there would be any benefit from such an exemption, asserting that a Schedule 5 listing was not a significant burden on a product which would have to be registered by APVMA anyway. Another Member was concerned that allowing such a cut-off could set a precedent whereby many products listed in Schedule 5 could also qualify for such exemptions. The Committee generally agreed, however, that the applicant had supplied appropriate data to support the 0.05 per cent exemption and that there was no reason not to support this proposal.

The Committee then discussed whether this exemption cut-off should be raised, as requested in the pre-meeting submissions, from 0.05 per cent to either 0.06 or 0.1 per cent. Several Members noted that the main drive for this requested cut-off increase was to avoid regulatory impact on a number of products currently marketed with

concentrations in this range. A Member asserted that the request seemed reasonable, noting that the minor eye irritancy observed at low concentration appeared to be a physical consequence of the formulation rather than a chemical effect. The Member asserted that the margin of exposure would not be significantly different in going from 0.05 to 0.1 per cent. The Committee generally agreed to exempt products containing 0.1 per cent deltamethrin from scheduling.

RESOLUTION 2010/58 - 5

The Committee decides to exempt preparations containing ≤ 0.1 per cent deltamethrin from the requirements of scheduling.

Schedule 5 – Amendment

DELTAMETHRIN – Amend entry to read:

DELTAMETHRIN:

(a) in aqueous preparations containing 5 per cent or less of deltamethrin when no organic solvent other than a glycol is present;

(b) in wettable granular preparations containing 25 per cent or less of deltamethrin when packed in child-resistant packaging each containing 3 grams or less of the formulation;

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

(d) in other preparations containing 0.5 per cent or less of deltamethrin,

except in preparations containing 0.1 per cent or less of deltamethrin.

Schedule 6 – Amendment

DELTAMETHRIN – Amend entry to read:

DELTAMETHRIN:

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

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

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

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

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

except when included in Schedule 5 or in preparations containing 0.1 per cent or less of deltamethrin.

Schedule 7 – Amendment

DELTAMETHRIN – Amend entry to read:

DELTAMETHRIN **except:**

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

(b) when in preparations containing 0.1 per cent or less of deltamethrin.

6.2 FORAMSULFURON

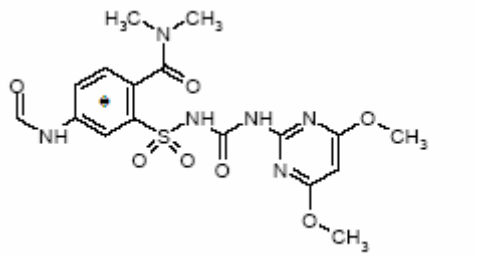
PURPOSE

The Committee considered the scheduling of foramsulfuron.

BACKGROUND

Foramsulfuron belongs to the sulfhydryl herbicides chemical class. Foramsulfuron inhibits the synthesis of amino acid in plants through inhibition of acetolactate synthase (ALS). This process results in slow or stunted plant growth and/or ultimate plant death. ALS catalyses the first step in the synthesis of the branched amino acids valine, leucine and isoleucine. Inhibition of ALS by sulfhydryl chemicals is only relevant in plants.

Foramsulfuron is the ISO approved common name for the chemical (IUPAC) 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl)urea. Foramsulfuron has the following chemical structure:



A number of sulfhydryl herbicides are currently in Schedule 5 (including ethoxysulfruon, halosulfuron-methyl, rimsulfuron and sulfometuron-methyl) or Appendix B (including mesolsulfuron-methyl, sulfosulfuron, triasulfuron and trifloxysulfuron).

DISCUSSION - SUBMISSIONS

XXXXX had prepared an evaluation report on an APVMA application by XXXXX to register the new active ingredient foramsulfuron and registration of the new product XXXXX containing XXXXX foramsulfuron. XXXXX. The evaluator has made the following recommendations:

XXXXX

Public Health Standards

- Neither an ADI nor ARfD for foramsulfuron has been established as it is not intended for use on food producing crops.
- Based on slight eye irritation observed in rabbits, the Committee may consider Schedule 5 appropriate for foramsulfuron. This recommendation is consistent with the scheduling of a number of chemicals (ethoxysulfruon, halosulfuron-methyl, rimsulfuron and sulfometuron-methyl) in this sulfhydryl herbicides class.

XXXXX

Members also noted the following from the evaluation report:

- There were no impurities of toxicological concern.
- The toxicology database consists of an array of laboratory animal (*in vivo*) and cell culture (*in vitro*) toxicity studies. These studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is acceptable, and the database is considered adequate to characterize the toxicity profile of foramsulfuron.

Toxicology findings from the evaluation for foramsulfuron are summarised below:

XXXXX

- Following oral administration in XXXXX, foramsulfuron was readily but poorly absorbed through the gastrointestinal tract and was rapidly excreted in the faeces and urine. The compound underwent limited metabolism with only two metabolites

detected in the excreta, with the parent compound being the most prevalent recovered compound.

- In a percutaneous study in XXXXX, foramsulfuron had low potential to be absorbed when applied as either an undiluted formulation concentrate XXXXX or an aqueous spray dilution XXXXX.
- Foramsulfuron showed no indication of being bioaccumulative.
- Foramsulfuron was of low oral XXXXX, dermal XXXXX, and inhalational toxicity XXXXX. It was a slight eye irritant in XXXXX, but neither a skin irritant in XXXXX nor a skin sensitiser in XXXXX.
- Repeat dosing of foramsulfuron in XXXXX, XXXXX and XXXXX did not cause any remarkable treatment related toxic effects. A reduction in body weight gain was noted in XXXXX. However, this very high dose finding was not observed in any other repeat dose studies in XXXXX and, thus, it is concluded that the changes in the body weight, though treatment related, have little relevance to humans. No other treatment related effects or clinical signs were observed in XXXXX at lower doses in XXXXX. No treatment related effects were observed in XXXXX-day dietary studies in XXXXX. There was no evidence of systemic toxicity during a XXXXX-day repeat dose dermal study with doses up to XXXXX. No treatment related effects were observed in XXXXX during a XXXXX month oral study.
- Foramsulfuron was largely not genotoxic *in vitro* and *in vivo* tests although there was some weak evidence of potential clastogenicity in a XXXXX.
- No treatment related effects, or indications of oncogenicity, were observed in XXXXX in chronic studies. There was no evidence of carcinogenicity in animals treated with foramsulfuron.
- It was not a reproductive or developmental toxin in XXXXX. Although significant decreased maternal body weight gain was observed in pregnant XXXXX in a developmental study, no developmental or teratogenic effects were observed.
- It was not a neurotoxin in XXXXX.
- Other sulfhydryl herbicides have been evaluated by XXXXX, including mesosulfuron, ethoxysulfuron, sulfosulfuron, azimsulfuron and rimsulfuron. Members of this group have low acute toxicity and are generally slight eye irritants. Treatment related effects observed during repeat dose studies are generally limited to higher doses. The target organs of this group of chemicals are generally the liver and kidneys and male reproductive organs. The sulfhydryl class of chemicals has no notable effects on reproduction and development nor is there any indication of carcinogenicity or genotoxcity. The toxicological profile of foramsulfuron is consistent with the other members of the sulfhydryl class.

Members also noted the following summary of the product toxicology findings from the evaluation report:

XXXXX

- The product had low acute toxicity via the oral XXXXX, dermal XXXXX and inhalation XXXXX routes in XXXXX. It was moderately irritating to the skin and a slight eye irritant in XXXXX.
- Under the conditions of XXXXX, foramsulfuron was not a skin sensitiser.
- In short-term studies, the toxicity effects were restricted to decreased body weight gain XXXXX in XXXXX receiving XXXXX in a XXXXX-day dietary study. No treatment-related effects were observed in similar studies in XXXXX.
- There was no evidence of systemic toxicity during a XXXXX-day repeat dose dermal study with doses up to and including XXXXX. There were no treatment–related effects observed in subchronic and chronic studies. A NOEL of XXXXX was identified in a XXXXX-day dietary study in XXXXX from these repeat dose studies.

Members also considered the following summary of the human risk assessment from the evaluation report:

- XXXXX. Bystander exposure may occur during application with boom spray if there is spray drift. Post-application exposure is not expected to occur XXXXX.

Occupational exposure

- Farmers and their employees will be the main users of the product. Workers may be exposed when opening containers, mixing/loading, application and cleaning up spills and equipment. The main route of exposure to the spray will be dermal and inhalational, with potential accidental ocular.
- For intermittent and infrequent occupational exposures (i.e. ≤ 5 days consecutively, ≤ 4 times in one year), the most appropriate NOELs for OHS assessment are drawn from short-term dermal studies of XXXXX days exposure or less. A XXXXX-day dermal study in XXXXX for foramsulfuron was submitted. Given the short term use pattern and lack of systemic toxicity in a XXXXX-day dermal toxicity in XXXXX a quantitative OH&S risk assessment was not required.
- Based on the low levels of toxicity in repeat dose studies, the use of personal protective equipment is not required.
- Based on the low toxicity exhibited in acute and repeat dose studies, there is no re-entry or re-handling risk. However, in the interest of best practice the applicant has recommended waiting until the spray has dried before entering treated areas.

Members also noted the following recommended hazard classification statements from the evaluation report:

Active

- Foramsulfuron is not listed on Safe Work Australia's Hazardous Substances Information System Database. Based on the toxicological assessment, foramsulfuron is not classified as a hazardous substance.

XXXXX

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (c) potential hazards and (d) the extent and patterns of use of a substance.

The Committee debated whether the eye irritancy warranted inclusion in Schedule 5. Several Members suggested that foramsulfuron was suitable for inclusion in Appendix B, asserting that the decision should be based solely on the characteristics of the substance and not the product, noting that the moderate skin irritation of the product was not likely due to the foramsulfuron component. They also asserted that scheduling should consider all the information on balance, and not be based on one toxicological parameter, noting that the only concern for foramsulfuron appeared to be slight eye irritancy. They suggested that APVMA labelling would be sufficient to address such toxicity if it was relevant to the end-use product.

A Member advised that foramsulfuron was considered in New Zealand last year, although the product also considered then was of a different formulation and had a different use pattern to that being proposed for Australia. In New Zealand it was decided that the eye irritancy for foramsulfuron was below the trigger for GHS classification and the Member suggested that this supported an Appendix B listing. Members noted that while the evaluator was aware of the GHS criteria, the evaluator considered that the eye irritancy of foramsulfuron to be an inherent hazard of the chemical material, causing irritancy as the active alone and in the end-use product, and it thus met, in the evaluator's opinion, the criteria for Schedule 5. Other Members disputed this conclusion, suggesting that the irritancy was too marginal for Schedule 5. The Committee noted that it was always difficult scheduling substances with only a slight irritancy concern.

A Member noted, however, that the irritation was observed for both the active ingredient and the end use product, and that the initial irritation observed was substantial. The Member further noted that the irritation persisted for up to 24 hours post instillation and did not resolve completely until two days after instillation. On the basis of persistency of irritation, and as it was likely that the irritation was inherent to the chemical, Members generally agreed that foramsulfuron should be included in Schedule 5.

RESOLUTION 2010/58 – 6

The Committee decided to include foramsulfuron in Schedule 5.

Schedule 5 – New entry

FORAMSULFURON.

6.3 MANDIPROPAMID

PURPOSE

The Committee considered the scheduling of mandipropamid

BACKGROUND

Mandipropamid is a compound belonging to the mandelic acid amide subgroup of the carboxylic amide fungicides. It exerts its effect by inhibiting the synthesis of phospholipids in fungi. Mandipropamid is the approved common name for the chemical 2-(4-chloro-phenyl)-N-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-prop-2-ynyloxy-acetamide (IUPAC).

DISCUSSION – SUBMISSIONS

XXXXX had prepared an evaluation report on an APVMA application XXXXX for the approval of a new technical grade active constituent (TGAC), mandipropamid. Data was also submitted seeking the registration of a new product, XXXXX containing XXXXX mandipropamid. XXXXX. The evaluator has recommended:

XXXXX.

Public Health Standards

- The ADI for mandipropamid was established at 0.05 mg/kg bw/day based on a NOEL of 5 mg/kg bw/day XXXXX and using a 100-fold safety factor.
- An ARfD was not necessary because mandipropamid has no significant toxicity after a single or few doses.
- Based on the acute toxicity profile, mandipropamid was considered to meet the requirements for a Schedule 5 chemical.

XXXXX.

Members also noted from the evaluation report:

- The data package on the TGAC consisted of acute oral, dermal and inhalational studies, skin and eye irritation studies and a skin sensitisation study on TGAC mandipropamid. Also provided were studies on toxicokinetics and metabolism, short term, subchronic and chronic (including carcinogenicity) repeat dose studies, genotoxicity (*in vitro* and *in vivo*), and developmental, reproductive and neurotoxicity studies.

- The toxicology studies were conducted in accordance with contemporary test guidelines. The data provided in the acute and repeat dose studies were relied on by the evaluator in considering whether the proposed use of the product would not be an undue health hazard to the public.
- XXXXX.

Toxicology findings from the evaluation are summarised below:

TGAC

XXXXX.

- Mandipropamid has low acute oral XXXXX, dermal XXXXX and inhalation XXXXX toxicity in XXXXX. It was a slight skin and eye irritant in XXXXX but was not a skin sensitiser in XXXXX.
- No treatment related systemic effects were observed in a repeat dose XXXXX dermal application study.
- Repeat dose studies XXXXX showed that the liver was the main target organ. XXXXX. Mandipropamid was not carcinogenic in XXXXX.
- Mandipropamid was not genotoxic in XXXXX studies. XXXXX. Mandipropamid was not a carcinogen and there was no concern for *in vitro* mutagenicity.
- There was no evidence that mandipropamid was a reproductive or developmental toxicant.
- There was no evidence that mandipropamid is neurotoxic.

Product XXXXX

XXXXX.

- The product had low acute oral XXXXX, dermal XXXXX, and inhalation toxicity XXXXX. It was a slight eye and skin irritant in XXXXX but was not a skin sensitizer in XXXXX.

XXXXX.

Selection of a NOEL for risk assessment

A NOEL for risk assessment was not required because:

- For mandipropamid the NOEL for dermal toxicity is 1000 mg/kg bw/d or greater (XXXXX), and there is no evidence of carcinogenic, genotoxic, reproductive, developmental or neurotoxic effects. The vapour pressure for mandipropamid is very low and inhalation of mandipropamid vapour is unlikely to present an inhalation hazard.

- On these bases, the evaluator has indicated that a quantitative risk assessment is not required and a NOEL for risk assessment was not established. Personal and protective equipment recommendations were only made for the acute risks (e.g. skin and eye irritation).

Risk management

Based on the proposed use pattern and toxicological characteristics XXXXX, the principal hazards will arise from skin and eye irritation if accidental contact is made when opening the containers and preparing the spray mix. XXXXX.

Members also noted that in the evaluation report the following regarding hazard classification:

- Mandipropamid is not listed on Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database. With the available toxicology information, the evaluator has determined that neither the active ingredient mandipropamid nor the product is hazardous according to the 2004 NOHSC *Approved Criteria for Classifying Hazardous Substances.*
- The evaluator also determined that the product did not need GHS classification and that a hazard alert symbol was not applicable.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety and (c) potential hazards.

The Committee debated the severity of the eye irritation and whether it was appropriate for Schedule 5. One Member asserted that the classification as an irritant appeared to be based on only slight irritation, and perhaps the overall risk didn't warrant scheduling. Other Members noted, however, that it was the extended duration of the irritancy observed that was of concern, rather than just the severity, and agreed to the irritancy classification. The Committee agreed that Schedule 5 was appropriate for mandipropamid.

The Committee also discussed the relevance of the eye irritancy of the product being considered when scheduling should ideally be substance based. This distinction was acknowledged by the Committee, but it was generally accepted that the irritancy of the product was probably relevant in this case as it was demonstrated that the eye irritancy was still a potential issue at lower concentrations. Similarly, skin irritation was also observed for the product. Members generally agreed, therefore that there was no basis for a low concentration cut-off at this time.

RESOLUTION 2010/58 – 7

The Committee decided to include mandipropamid in Schedule 5.

Schedule 5 - New entry

MANDIPROPAMID.

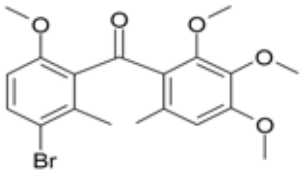
6.5 METRAFENONE

PURPOSE

The Committee considered the scheduling of metrafenone.

BACKGROUND

Metrafenone is the approved common name of the chemical 3'-bromo-2,3,4,6'-tetramethoxy-2',6-dimethylbenzophenone (IUPAC). Its chemical structure is as follows:



Metrafenone is a benzophenone fungicide. Metrafenone interferes with hyphal morphogenesis, polarises hyphal growth and the establishment and maintenance of cell polarity. Metrafenone likely disturbs a pathway regulating organisation of the actin cytoskeleton. Preventive treatments reduce germination and block development and curative treatments rapidly affect fungal survival at low concentrations (Opalski KS, Kogel K-H, Grossmann K, Kohle H & Huckelhoven R, 2006, 'Metrafenone: studies on the mode of action of a novel cereal powdery mildew fungicide', *Pest Management Science*, vol 62(5), pp. 393-401).

DISCUSSION - SUBMISSIONS

XXXXX had prepared an evaluation report on an APVMA application XXXXX for the approval of a new technical grade active constituent (TGAC), metrafenone. Data was also submitted to support registration of the product XXXXX containing XXXXX metrafenone. The evaluator has recommended:

XXXXX.

Public Health Standards

- ADI for metrafenone was established at 0.25 mg/kg bw/day based on a NOEL of 24.9 mg/kg bw/day in a XXXXX study and using a 100-fold safety factor.
- The ARfD for metrafenone was not established and there was not sufficient data to enable an ARfD to be set.
- Metrafenone has low acute toxicity, it is non-irritating to eyes and skin, and has no skin sensitization potentials. Notwithstanding its low acute toxicity, metrafenone has

shown carcinogenic potential in XXXXX (irreversible toxicity). Consequently, the Committee may consider it appropriate to include metrafenone in Schedule 7. Alternatively, Schedule 6 may be more appropriate since carcinogenicity in XXXXX occurred at high dose levels and exposure to such levels is unlikely to be encountered considering the proposed product use pattern.

XXXXX

Members also noted the following from the evaluation report:

- The data package consisted of acute oral, dermal and inhalational studies, skin and eye irritation studies and a skin sensitisation study on TGAC metrafenone. Also provided were studies on dermal absorption, toxicokinetics and metabolism, short term, subchronic and chronic (including carcinogenicity) repeat dose studies, genotoxicity (*in vitro* and *in vivo*), and developmental, reproductive and mechanistic studies.
- The evaluator indicated that there appeared to be an extensive body of information on benzophenone, the chemical 'backbone' of metrafenone.
- It was claimed that metrafenone had a unique (but undescribed) mode of action. Members noted the 2006 publication by Opalski *et. al*. which examined the mode of action of metrafenone.
- Metrafenone and associated compounds have not been registered in Australia. However, metrafenone has been registered in the Europe Union and Korea and there are registered products containing metrafenone in these countries.

Toxicology findings from the evaluation are summarised below:

TGAC

XXXXX.

- Metrafenone was well absorbed XXXXX after oral administration. Metrafenone is extensively metabolised in tissues. XXXXX Metrafenone was poorly distributed in tissues. XXXXX.
- XXXXX.
- Metrafenone has low acute oral XXXXX, dermal XXXXX and inhalational XXXXX toxicity in XXXXX. The compound was not a skin or eye irritant in XXXXX and not a skin sensitiser in XXXXX. Because benzophenone (the parent compound for metrafenone) was used primarily as a photo-initiator and fragrance enhancer, an additional study provided showed that metrafenone does not possess phototoxic or photoallergenicity potential in XXXXX.
- Repeat dose studies XXXXX indicated that the liver is the main target organ in all the species studied. XXXXX.

- In an XXXXX month dietary oncogenic study in XXXXX a statistically significant increase in the incidence of hepatocellular adenoma occurred in XXXXX at study termination. A marginal and insignificant increase in hepatocellular carcinoma was also seen in the same dose group XXXXX.
- Based on increased liver weight and discoloured mesenteric node in XXXXX, as well as an increase in the incidence of hepatocellular hypertrophy and chronic nephropathy in XXXXX, the systemic NOEL XXXXX was 250 ppm XXXXX. The NOEL for carcinogenicity was 1000 ppm, XXXXX.
- In a XXXXX month dietary study in XXXXX, metrafenone administration increased the incidence of hepatocellular adenomas in XXXXX.
- Based on the effects of metrafenone administration on the body weight gain in XXXXX, and changes in clinical chemistry parameters, organ weights and liver and/or kidney histopathology changes in XXXXX, the systemic NOEL from a XXXXX month XXXXX study was 500 ppm XXXXX. The NOEL for carcinogenicity was 500 ppm, XXXXX.
- A survey of literature indicated that benzophenone possesses carcinogenic activity in F344/N rats and B6C3F1 mice at low doses and it appears that the inherent carcinogenicity potential of metrafenone originates from its parent compound (benzophenone). The evaluator concluded that metrafenone is a potential carcinogen in rodents at high doses.
- Metrafenone was not mutagenic or genotoxic *in vitro* and was not genotoxic *in vivo*.
- Metrafenone was not a reproductive toxicant in XXXXX, nor a developmental toxicant XXXXX.

Formulated product

- The formulated product had low acute oral XXXXX, dermal XXXXX and inhalational XXXXX toxicity in XXXXX. It was not a skin or eye irritant in XXXXX and not a skin sensitiser in XXXXX.

Members also noted the following regarding exposure and risk:

- XXXXX.
- Bystander exposure may occur if members of the public walk past an area at the time of treatment with the product or during entry into treated areas. Bystander exposure is likely to be lower than that of workers.
- Workers may be exposed to the product when opening containers, mixing/loading, application and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalation, although ocular exposure is also possible.
- Professional and contract workers in farms usually travel from farm to farm to carry out spraying operations and, thus, may potentially be exposed to this product all year

round (i.e. chronic exposure). As the most likely route of exposure to the product is dermal and inhalational, and the duration of exposure is expected to be chronic (to protect professional/contract workers), the most appropriate studies from which to choose a NOEL for OHS risk assessment purposes are long-term repeat-dose dermal and inhalational studies.

- Metrafenone was a new active ingredient and no repeat-dose dermal or inhalational studies are available. The lowest NOEL of the three long-term studies provided was 24.9 mg/kg bw/d in XXXXX. This NOEL was based on the observation of effects on the liver and kidney. Further, in a submitted XXXXX toxicokinetic study, orally administered metrafenone was well absorbed in XXXXX and, therefore, no adjustment had been made for gastrointestinal absorption. Therefore, the NOEL used for OHS assessment was 24.9 mg/kg bw/d.
- XXXXX.
- The evaluator noted that as metrafenone was not genotoxic *in vivo*, a health based limit can be established for the benign tumours. A NOEL of 24.9 mg/kg bw/day was established from a XXXXX-month dietary XXXXX, and was considered appropriate for risk assessment purposes.
- XXXXX.

Members also noted the following regarding hazard classifications:

- Metrafenone is not listed on Safe Work Australia's Hazardous Substances Information System Database. With the available toxicology information, the evaluator had determined that TGAC metrafenone XXXXX are classified as hazardous substances according to 2004 NOHSC *Approved Criteria for Classifying Hazardous Substances*, with the following risk phrases: R40 (Carcinogenic Category 3) 'Limited evidence of a carcinogenic effect'.
- Classification as a Category 3 carcinogen was considered more appropriate by the evaluator than Category 2, as the observed liver tumours seen in XXXXX are benign (i.e. hepatocellular adenomas), and in XXXXX were seen at a dose level XXXXX while in XXXXX were only seen at dose levels exceeding the 'maximum tolerated dose'. XXXXX. Furthermore, metrafenone did not exhibit a mutagenic or genotoxic potential *in vitro*, or a genotoxic potential *in vivo*.

XXXXX.

Applicant's response to the evaluation report

XXXXX responded to the evaluation report by arguing that the Weight-of-Evidence (WOE) based on metrafenone's mammalian toxicological profile supported classification as a borderline case between Schedule 5 and Schedule 6. Moreover, it was suggested that the WOE supports metrafenone's classification as a borderline case between "No Classification" (excluding a concern for humans) and R40 (Carc. Cat. 3) (limited evidence of a carcinogenic effect).

Members also noted the following from the applicant's response:

- Reiterated the low acute toxicity of both the TGAC and formulated product. The applicant therefore argued that, for the normal use pattern (relatively low concentration of the end-use product), humans are potentially exposed to only a low level of hazard.
- Asserted that, although long-term, repeated dietary administration XXXXX resulted in "irreversible toxicity," its tumourigenic response occurred only at high dose levels XXXXX. Such a regimen of high dosages over a prolonged period presents only very low risk to humans who are highly unlikely to be exposed to these extreme doses, and never likely to be exposed for such a prolonged period of time to such high doses.
- Limited evidence of a carcinogenic effect (WOE approach) probably excludes a concern for man. Chronic testing with metrafenone revealed a limited oncogenic effect in the liver for XXXXX. There was an increased incidence for benign hepatocellular adenoma in XXXXX at XXXXX. Also, there was an increased incidence for benign hepatocellular adenoma and combined hepatocellular adenoma/carcinoma in XXXXX at XXXXX. The applicant argued that, in general, XXXXX are considered to be more sensitive to the induction of liver tumours than humans, and only XXXXX liver tumours have been identified in metrafenone studies.
- XXXXX.
- Metrafenone did not demonstrate genotoxic potential when tested in a battery of genotoxicity assays. The compound also did not show initiating potential when tested in a specific mechanistic study in XXXXX. Asserted that the proposed mechanism of action XXXXX is a mechanism which is well accepted as demonstrating a progression to liver tumors in XXXXX by a non-genotoxic process.
- Metrafenone has not been associated with an increased incidence of neoplastic findings in any other organ or tissue, as tested in long-term toxicity studies in XXXXX. No effects suggesting hormonal disturbance have been identified. Few effects other than relating to the liver have been identified (the remaining effects are mostly found in the kidney), and consequently, there are no other obvious mechanisms by which the tumours in the liver might be secondary to effects occurring in a different organ or tissue.
- The applicant also noted that a German review of metrafenone concluded that the classification and labeling with R40 is not considered necessary. The liver tumours in XXXXX long-term toxicity study were observed only at dose levels that were liver toxic. According to the IPCS Conceptual Framework, the human relevance is limited since a high margin of safety (>1000) exists between exposure and tumorigenic dose level.
- The applicant additionally noted a United Kingdom conclusion that metrafenone need not be classified for carcinogenicity. A similar conclusion was reached by the European Food Safety Authority in its Scientific Report (2006) "Since the mechanism of tumour formation in rats and mice is linked to excessive and continuous exposure

to metrafenone, it was decided not to propose a cancer classification for metrafenone in Europe".

- The applicant concluded that because prolonged high dose levels required to elicit irreversible toxicity in humans would likely not be encountered in a normal exposure setting, metrafenone's classification of Schedule 5 (rather than Schedule 6) would be appropriate. Asserted that metrafenone is not considered to pose a carcinogenic risk to humans. The WOE does not support a cancer classification, mainly because the prolonged high dose levels necessary to elicit a carcinogenic response in humans would not be encountered in a normal exposure setting, thus supporting "No Classification" (which excludes a concern for man).

Pre-meeting submission

XXXXX reiterated the low acute toxicology of the product and argued that there was no other significant toxicity. Schedule 5 was proposed but it was conceded that the Committee may consider a Schedule 6 listing as a worst-case scenario (asserting that Schedule 7 was inappropriate). Should a Schedule 6 parent entry be pursued, it was requested that the Committee consider a 50 per cent cut-off to Schedule 5, arguing that this was more appropriate XXXXX.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (c) potential hazards and (d) extent and patterns of use.

Members noted that the key issue of concern with regard to metrafenone appeared to be carcinogenicity. One Member noted that, although carcinogenicity was observed in two species (which would normally indicate a Schedule 7 entry as being warranted), the carcinogenic response was only observed at very high dose rates and/or very high exposure rates. The Committee debated the relevance of the classification of metrafenone as a carcinogen to scheduling when such a high dose was required, and when, in practice, an individual would be highly unlikely to be exposed to such amounts. The Committee generally agreed, on the basis of the very low risk of being exposed to the quantities required for carcinogenicity, that the weight of evidence supported a Schedule 6, rather than Schedule 7 metrafenone parent entry.

A Member also asserted that, with such a limited carcinogenicity risk, and no other significant toxicological concern, that consideration should be given to the request of the pre-meeting submission for a cut-off to Schedule 5 for preparations containing 50 per cent or less or metrafenone. The Member also noted that metrafenone was not intended for domestic use. Another Member remained concerned, however, that the proposed MOA of metrafenone may pose a particular risk to people who over use alcohol. Members generally agreed that this specific concern would largely relate to individual product use/formulation and as such was one best addressed through labelling requirements resulting from the APVMA's product approval process rather than by

scheduling. The Committee agreed that a cut-off to Schedule 5 for 50 per cent of less of metrafenone was appropriate.

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The Committee decided to include metrafenone in Schedule 6, with a cut off to Schedule 5 for preparations containing 50 per cent or less of metrafenone.

Schedule 5 – New entry

METRAFENONE in preparations containing 50 per cent or less metrafenone.

Schedule 6 – New entry

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

6.6 SAFLUFENACIL

PURPOSE

The Committee considered the scheduling of saflufenacil.

BACKGROUND

Saflufenacil is a member of the pyrimidindiones group of herbicides. Its mode of action is through a process of membrane disruption which is initiated by the inhibition of the enzyme protoporphyrinogen oxidase (PPO). This inhibition interferes with the chlorophyll biosynthetic pathway. The chemical can be rapidly absorbed by roots and foliage of the plant, and results in membrane damage and eventually plant death by inhibiting the PPO enzyme in the presence of light. Saflufenacil provides rapid burn-down of emerged broadleaf weeds.

Other pyrimidindione herbicides include benzfendizone and butafenacil. Benzfendizone is not registered in Australia. Butafenacil is in Appendix B.

At the June 2009 meeting, the Committee decided to include saflufenacil in Schedule 7. The Committee particularly noted that saflufenacil increased skeletal malformations (bent scapula) in the absence of any significant signs of maternal toxicity. The Committee was concerned with the bent scapula effect, noting that this was an irreversible effect and was a highly unusual developmental toxicity marker.

At the October 2009 meeting, the Committee considered post-meeting submissions, which included new developmental toxicity data, requesting inclusion of saflufenacil in Schedule 6. The Committee noted the new developmental toxicity data asserted that there were marked interspecies differences with regard to PPO inhibition by saflufenacil. The Committee particularly noted that the study considered only salfufenacil's role in inhibiting one enzyme (PPO), yet other PPO inhibitors had not produced the bent scapula

effect. It was therefore argued that it was not possible to conclude that only this particular enzyme was responsible for the developmental toxicity effect. The Committee decided that the June 2009 Schedule 7 decision remained appropriate until the new data on developmental toxicity had been evaluated through the usual APVMA process.

DISCUSSION - SUBMISSIONS

XXXXX had updated its previous evaluation report to include new developmental toxicity data on an application to APVMA by XXXXX to register XXXXX, containing saflufenacil. The evaluator made the following new recommendations:

- Saflufenacil had low acute toxicity, it was a slight skin irritant and a minimal eye irritant, and had no skin sensitisation potentials. Notwithstanding its low acute toxicity, saflufenacil had shown developmental toxicity potential in XXXXX (irreversible toxicity) but not in XXXXX. Consequently, the Committee may consider it appropriate to retain saflufenacil in Schedule 7. Alternatively, Schedule 6 may be more appropriate since developmental toxicity was not seen in XXXXX and *in vitro* data indicates that saflufenacil is a PPO inhibitor and that XXXXX are significantly more sensitive to this effect than XXXXX. However, the mode of action (MOA) for saflufenacil induced skeletal malformation has not been established, though there is limited evidence to suggest that inhibition of PPO may not be relevant to the MOA.

The following recommendations remain the same as per the October 2009 consideration:

XXXXX.

Public Health Standards

- The ADI for saflufenacil was established at 0.017 mg/kg bw/d based on a NOAEL of 5 mg/kg bw/d (which is also the NOEL) in a developmental XXXXX study and using a 300-fold safety factor.
- The ARfD for saflufenacil was established at 0.017 mg/kg bw/d based on a NOAEL of 5 mg/kg bw/d (which is also the NOEL) in a developmental XXXXX study and using a 300-fold safety factor.

XXXXX.

New toxicity consideration

Members noted that the evaluation report was essentially the same as that considered in June and October 2009 with the exception of the evaluation of new data that disputed the relevance of the developmental toxicity findings in XXXXX. The new data investigated the relative inhibitory effects of saflufenacil, as well as oxyfluorfen and butafenacil, on PPO activity in liver mitochondrial fractions obtained from XXXXX. Members particularly noted the following from the evaluation report:

- The relative inhibitory potency of saflufenacil in XXXXX liver mitochondria was approximately XXXXX higher relative to the XXXXX. Much higher differences in relative inhibition were seen with XXXXX, when compared to XXXXX.
- The *in vitro* data indicated that XXXXX were significantly more sensitive to PPO inhibition than XXXXX, which was consistent with the *in vivo* developmental findings in XXXXX.
- The *in vitro* study provided no evidence for the MOA of saflufenacil induced skeletal malformation.
- Butafenacil and oxyfluorfen are both more potent PPO inhibitors than saflufenacil *in vitro*, but skeletal effects were only seen with oxyfluorfen, and in both XXXXX, in the presence of marked maternal toxicity.
- The divergent findings in XXXXX developmental studies with butafenacil and oxyfluorfen suggest that inhibition of PPO may not be relevant to the MOA for saflufenacil induced skeletal malformation.

- The evaluator indicated that due to the occurrence of foetal toxicity in a developmental toxicity study, including skeletal malformations in the absence of maternal toxicity, an extra safety factor was consider necessary to protect women of child bearing age. The choice of an appropriate extra safety factor value was undertaken using expert judgement and consideration of the following observations:
  - Compared to concurrent controls, there was a statistically significant decrease in mean foetal body weight (both sexes combined) of XXXXX in the mid XXXXX and high dose XXXXX groups.
  - A statistically significant increase in incomplete ossification of the nasus in the mid XXXXX and high dose XXXXX groups.
  - A XXXXX incidence of bent scapula at the mid dose and 5 incidences at the high dose XXXXX.
  - Bent scapula and incomplete ossification of the nasus had not been observed in a historical database of XXXXX foetuses. However, it was noted and accepted that while the observed decrease in body weight gain is treatment related (i.e. followed a dose response relationship) the decrease of XXXXX at the mid dose was close to the average statistical weight of the testing facility and therefore may simply reflect biological variation.
  - Overall, the treatment related findings at the mid dose of XXXXX were limited and minimal with regards to their incidence and toxicological nature. This suggests that XXXXX was likely to be close to the NOAEL/LOAEL threshold for developmental toxicity. Further, the NOAEL (and NOEL) of XXXXX for developmental toxicity is 12-fold lower than the identified maternal NOAEL of XXXXX, at which the observed maternal effects (increased porphyrin and urobilinogen in the plasma) were not considered adverse but are indicators of exposure.

- The evaluator concluded that in consideration of the above, an extra 3-fold safety factor is considered appropriate for derivation of relevant health standard values.
- Members particularly noted that the data on this end point was provided only for the TGAC, so there was little basis for suggesting a potential cut-off.

Previous toxicity consideration

Members also recalled the following from the evaluation report which remains unchanged to that in the version considered at June and October 2009 meetings:

- XXXXX. The database supplied by the applicant was considered to be adequate for the purposes of risk assessment.
- The evaluator advised that, given the difficulties in determining whether some observed effects were necessarily adverse, Australian toxicological assessments have usually used the terms NOEL and LOEL instead of NOAEL and LOAEL XXXXX. However, as the XXXXX report relied heavily on XXXXX, the evaluator adopted a NOAEL and LOAEL approach using scientific justification for their adoption. It was noted that for developmental toxicity the NOAEL value was also a NOEL.

Technical Grade Active Constituent

The TGAC hazard characterisation from the evaluation is summarised below:

XXXXX.

- Based on the findings of the acute toxicological studies evaluated, TGAC saflufenacil is of low acute toxicity by the oral XXXXX, dermal XXXXX, and inhalation routes XXXXX. It was minimally irritant to eyes and slightly irritating to skin in XXXXX. Skin sensitisation testing in XXXXX did not demonstrate a potential for skin sensitization.
- Increased stillborns and XXXXX mortality during the early phase of lactation, together with reduced XXXXX body weight gains were observed at XXXXX in a XXXXX-generation reproduction study in XXXXX. However, saflufenacil did not affect reproductive performance or the reproductive system. Conversely, increased abortion was seen in a XXXXX developmental study but only at a dose level that caused severe maternal toxicity (e.g. mortality in XXXXX).
- In short and long-term dietary toxicity studies in XXXXX, saflufenacil induced microcytic hypochromic anaemia affecting red blood cell parameters. The organs affected were the liver, spleen, and bone marrow.

Saflufenacil is not listed in Safe Work Australia's Hazardous Substances Information System (HSIS) Database (2009). However, based on the available toxicological information, the evaluator has classified saflufenacil as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004),

with the following risk phrase: Possible risk to harm to the unborn child (at concentrations ≥ 5 per cent).

The GHS for saflufenacil is:

NOHSC Classification	**GHS Classification**	**Hazard Communication**
Possible risk of harm to the unborn child	Reproductive toxicity Category 2	Warning  Suspected human reproductive toxicant (developmental effects)

Formulated products

The formulated product – XXXXX hazard characterisation from the evaluation is summarised below:

XXXXX.

- XXXXX is of low acute oral XXXXX, dermal XXXXX and inhalational toxicity XXXXX. It was a slight skin and eye irritant in XXXXX, but was not a skin sensitiser in XXXXX.

XXXXX.

The formulated product – XXXXX hazard characterisation from the evaluation is summarised below:

XXXXX.

- XXXXX is of moderate to high acute oral toxicity XXXXX, and low dermal XXXXX and inhalational XXXXX toxicity in XXXXX. It was a moderate skin and severe eye irritant in XXXXX. It showed skin sensitisation potential XXXXX.

XXXXX.

Members additionally noted the following regarding exposure and risk for the products (the evaluator had conducted both exposure and risk assessments for salfufenacil based on the Schedule 7 conditions i.e. assuming no public exposure):

Public exposure

- The evaluator indicated that although small packages of the products were available, the inclusion of saflufenacil in Schedule 7 will prevent access to the products by the general public.

- XXXXX. The evaluator indicated that based on the exposure risk assessment to workers during and after application, it is unlikely that the applications conducted by specialised users would pose any exposure risks to by-standers during application and the public's re-entry to the treated areas. The evaluator therefore concluded that no particular risk management measures were considered necessary.
- XXXXX.

Occupational exposure

- Workers may be exposed to the product when opening containers, mixing / loading, application, and cleaning up spills, maintaining equipment and entering treated areas. The main route of exposure to the products will be dermal, inhalation as well as ocular contact.
- The evaluator commented that the inclusion of safluenacil in Schedule 7 required special precautions during manufacture, in particular, women of child bearing age are advised not to be associated with manufacture and formulation due to potential developmental toxicity.

Applicant's responses to the evaluation report.

The applicant submitted two pre-meeting submissions with the second being an amendment to the first. Members particularly noted the following from these submissions:

- Indicated that it did not support the human health risk assessment in the evaluation report, because this was conducted in the context of saflufenacil as a Schedule 7 substance. The submission further stated that the evaluation was based on the hazard of saflufenacil in isolation, without considering the overall health risk following exposures according to the proposed use patterns.
- Argued that it did not support a Schedule 7 listing for both saflufenacil products and instead proposed a Schedule 6 listing. The applicant listed the following reasons:
  - XXXXX;
  - both XXXXX were not intended for domestic market supply;
  - the potential risk associated with the use of the products by workers was low provided the product was used according to the proposed label directions with recommended protective measures. Both products were intended only for XXXXX and in many instances would only be used once or twice per year, therefore repeated and long term exposure to saflufenacil is unlikely;
  - the US Environmental Protection Authority has granted 'Reduced Risk' status for saflufenacil. This will reduce or replace the use of other environmentally hazardous chemicals such as atrazine and paraquat;
  - asserted that XXXXX are significantly more sensitive to PPO inhibition than humans;

- while the *in vitro* study does not directly link PPO inhibition potency with skeletal malformations as observed with saflufenacil, it is known that PPO inhibitors cause anaemia and other haematological effects. Anaemia can lead to skeletal malformations therefore it is considered that there is a link between PPO inhibition and the skeletal malformations. The developmental period of exposure, as well as its duration and severity, determines the extent of embryonic cell damage caused by maternal anaemia and resulting hypoxia. The anaemia caused by saflufenacil is not severe, however, was probably of sufficient duration and degree to cause the observed developmental effects;
- conceded that there was an apparent inconsistency in the *in vitro* study. Other PPO inhibitors included in the *in vitro* study have not been shown to cause developmental effects *in vivo*, despite their high potency in inhibiting PPO *in vitro*. Argued, however, that there are many factors, such as metabolic activation or detoxification, reactivity and affinity of the substrate, and degree of porphyrin accumulation / excretion, that occurred *in vivo* that were not replicated in the *in vitro* study; and
- asserted that factors for scheduling decisions must be considered as a whole in determining the public health risk. Based on the use patterns proposed for saflufenacil and the label changes, the applicant requested the Committee re-consider the exposure as part of the scheduling process.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) risks and benefits, (c) potential hazards, (d) the extent and patterns of use and (f) the need for access to a substance.

The Committee generally agreed that the most significant endpoint of concern for scheduling was the potential developmental toxicity of saflufenacil, noting that the relevance of the observed effects to human was the main issue in dispute. A Member also reiterated that the US EPA had allocated a "Reduced Risk" status for saflufenacil.

While it was highly concerning that saflufenacil had been observed to cause severe malformations in the foetus (bent scapula) without concomitant maternal toxicity, several Members noted that this had only been observed in one species and questioned the significance of this effect and its relevance to humans. Another Member asserted that had the bent scapula effect been observed in more than one species, saflufenacil would likely have been considered a human reproductive toxicant, but with results in only one species, this was not a high intensity signal of concern.

A Member asserted that if the human reproductive concern was not particularly relevant to humans (and in any case may be reduced by labelling from the registration process), then the toxicological profile of saflufenacil (low acute oral, dermal and inhalational toxicity) suggested a Schedule 6 classification. Particular reference was made by the Member to the need for access, noting that saflufenacil was effective against resistant

weeds and therefore it had the potential to replace various highly toxic herbicides such as paraquat or atrazine. Another Member asserted, however, that although bent scapula was exhibited in only one species, the effect was dose related and occurred at two doses in the absence of maternal toxicity, and therefore should be considered as a significant concern for human reproductive toxicity.

Several Members also remained concerned that there was uncertainty regarding the mode of action for the bent scapula effect, noting that it is always difficult to extrapolate effects in a single species to human risk. In particular, the applicant argued that this effect would not be a risk for humans relied on data that demonstrated that there were marked interspecies differences with regard to PPO inhibition by saflufenacil. However, this relied on an assumed central role of PPO inhibition in causing the bent scapula effect. Several Members remained unconvinced that this association had been adequately established, noting:

- other PPO inhibitors had not produced bent scapula effect;
- the effect is a rare event in comparison to the historical database;
- while arguments have been made by the applicant that saflufenacil caused anaemia (through PPO inhibition) and that this could lead to skeletal malformations, a Member instead argued that it may be possible that saflufenacil is having an effect on scapula ossification through some other mechanism, not necessarily related to PPO inhibition. The Member asserted that as the mode of action for bent scapula is not known it is probably best to be cautious when attributing significance to this effect;
- even though the effect was only observed in a single species, it was observed at doses well below maternal toxicity levels and the effect exhibited a clear dose response; and
- therefore seemed to be a real effect with unknown mode of action.

Members generally agreed that, while only observed in one species and therefore not a clear human developmental hazard, on balance the uncertainty on the mode of action giving rise to the bent scapula effect supported a careful approach until such time as more robust arguments could be presented to reassure the Committee that this was not a significant risk to human health.

RESOLUTION 2010/58 - 9

The Committee confirmed that the current scheduling of saflufenacil remained appropriate.

6.7 SODIUM LAURYL SULPHATE

PURPOSE

The Committee considered the scheduling of sodium lauryl sulphate.

BACKGROUND

Sodium lauryl sulphate (SLS) is the approved ISO common name for the chemical sodium dodecyl sulphate (IUPAC). The chemical structure has a tail of 12 carbon atoms, attached to a sulphate group, giving the molecule the amphiphilic properties required of a detergent.

SLS is an anionic surfactant used in emulsifiable and suspension concentrates, liquid tablet and wettable powder formulations. SLS has a long history of use in industry, personal care products, as a pharmaceutical excipient and as a food additive. SLS has been used in cosmetics including shampoos and was listed on the Australian Inventory of Chemical Substances.

DISCUSSION - SUBMISSIONS

XXXXX prepared an evaluation report on an APVMA application by XXXXX for the approval of a new technical grade active constituent (TGAC), sodium lauryl sulphate. The applicant was also seeking registration for a new product XXXXX containing SLS XXXXX. The evaluator recommended:

XXXXX.

Public Health Standards

- The ADI for SLS was established at 0.1 mg/kg bw/d based on a NOEL of 100 mg/kg bw/d from a 28-day rat oral study and using a safety factor of 1000.
- No ARfD for SLS has been established and no suitable data was available to enable an ARfD to be set.
- Based on its oral acute toxicity and severe eye and skin irritation potential, SLS is recommended to be included in Schedule 6.

Label Statements

- New statements, including 'Will damage skin and eyes' and 'Attacks skin and eyes'.
- General Safety Precaution Statements also include 'Avoid contact with the eyes and skin', 'If product on skin, immediately wash area with soap and water' and 'If product in eyes, wash it out immediately with water'.

Members also noted from the evaluation report:

- No toxicological studies for SLS were submitted by the applicant. The toxicity assessment was prepared based on information primarily from the 'National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Existing Chemicals Information Sheet – Sodium Lauryl Sulphate, 9 October 2007', 'International Chemical Safety Card 0502' for SLS, International Programme on Chemical Safety, August 1997 and published literature including a 'Cosmetic Ingredient Review 1983'

provided by the applicant. The evaluator emphasised that a full independent hazard assessment on SLS has not been conducted by XXXXX.

[Members noted that the Cosmetic Ingredient Review 1983 is one of a series of Annual Reviews of Cosmetic Ingredient Safety Assessments. This particular review was published in the Journal of American College of Toxicology, 2(7):127-181, and assessed SLS comprehensively.]

- XXXXX.

Toxicological findings from the evaluation report are summarised below:

TGAC

Absorption, distribution, metabolism and excretion in mammals	
No data available	
Acute toxicity	
Rat oral LD_{50} (mg/kg bw)	1200
Rat dermal LD_{50} (mg/kg bw)	No data
Rabbit dermal LD_{50} (mg/kg bw)	Approximately 600
Rat inhalation 4-hr LC_{50} (mg/m^3)	>3900 (one hour exposure)
Skin irritation	Severe irritant
Eye irritation	Severe irritant
Skin sensitization	Unknown, but unlikely to be sensitising
Short-term toxicity	
Target/critical effect	Liver toxicity
Lowest relevant oral NOEL (mg/kg bw/d)	100
Lowest relevant dermal NOEL mg/kg bw/d)	No data
Genotoxicity	Unlikely to be genotoxic *in vitro* or *in vivo*
Long-term toxicity	No data available
Carcinogenicity	No evidence of a carcinogenic potential
Reproductive toxicity	Not a reproductive toxicant
Developmental toxicity	Not a developmental toxicant.

- SLS is harmful by the oral route (LD_{50} 1200 mg/kg bw) in rats, and by the dermal route in rabbits and guinea pigs (LD_{50} = ~600 mg/kg bw and >1200 mg/kg bw, respectively). A LC_{50} of greater than 3900 mg/m^3 following a one hour exposure has been reported for rats.
- SLS was shown to be a slight, moderate and severe eye irritant in rabbits after 1 hour at 2 2, 10 and 20 per cent, respectively. Eye irritation was resolved after 72 hours with 2 per cent SLS, while irritation persisted for at least 7 days after treatment with 10 and 20 per cent SLS.
- In a separate study, SLS was shown to be a slight, moderate and severe eye irritant in rabbits after 1 hour at 1.25, 2.5-5 and 10-20 per cent, respectively. However, immediate rinsing after ocular instillation significantly decreased irritation.

- SLS was shown to be a slight, moderate and severe skin irritant in rabbits 1 hour after topical application of 1, 5 or 20 per cent SLS, respectively. Skin irritation has been observed in clinical studies in humans. In the human 4-hour patch test for irritation, SLS is used at 20 per cent as a positive control to identify substances or preparations that would be on the borderline for classification as irritant. SLS was also reported to irritate the respiratory tract and oral mucosa, especially in individuals predisposed to recurrent mouth ulcers.
- There are no data available on skin sensitisation; however, given the long history of use in cosmetics, it is unlikely that SLS will cause skin sensitisation.
- A 28-day study by oral gavage was conducted in rats (10/sex/group) treated at 0, 30, 100, 300 or 600 mg/kg bw/d SLS. Two deaths occurred at 600 mg/kg bw/d and consequently the high dose was reduced to 300 mg/kg bw/d after 10 days of treatment. Decreased food consumption and bodyweight gains were seen at 300 mg/kg bw/d. Ulceration in the stomach was also observed at this dose. Increased liver weight was observed in females at 300 mg/kg bw/d. The NOEL was 100 mg/kg bw/d.
- SLS (99 per cent) was administered to rats (10/sex/group) at dietary concentrations of 0, 59, 116, 230, 470, 950 or 1900 mg/kg bw/d for 13-weeks (unreferenced study summary provided by the applicant). One female at 230 mg/kg bw/d was sacrificed at 4 weeks due to severe bodyweight loss. Serum alkaline phosphatase (ALP) was increased at 470 mg/kg bw/d and higher. This was correlated with increased relative liver weights in both sexes at the same doses. The NOEL was 116 mg/kg bw/d.
- The evaluator also provided the following summary of the derivation of particular parameters:

Summary	**Comments**
ADI (mg/kg bw/day)	A NOEL of 100 mg/kg bw/d from a 28-day rat oral study was selected for establishing an ADI. By applying a 1000-fold safety factor (10-fold safety factor for inter-species variability, 10-fold safety factor for intra-species variability, and a 10-fold safety factor for uncertainties due to an inadequate toxicological database and using a short-term study), the ADI for SLS was 0.1 mg/kg bw/d.
ARfD (mg/kg bw)	Not established due to a lack of data
NOEL for OHS Risk Assessment	Not established due to low exposure pattern and estimated toxicological profile of SLS and the product

- SLS was not a mutagenic or clastogenic *in vitro* bacterial and mammalian cells and was negative in a micronucleus assay in mice.
- SLS was not carcinogenic in Beagle dogs in the only study available.
- SLS was not a reproductive or developmental toxicant.

Human safety experience

- The Cosmetic Ingredient Review of 1983 contained cosmetic experience submissions for shampoos containing SLS. The data are shown below:

Per cent SLS present in shampoo	Sales of shampoo per year in the USA	Total number of applications per year in the USA	Number of safety-related complaints
10	390,000 units	8,580,000	None in two years
14.5	Not reported	200,000	17 in 7 years
30	398,000 units	4,852,620	One in 2 years

- The evaluator further advised that the USFDA list SLS as a food additive and had exempted it from the requirement of a food additive tolerance. They also consider SLS as Generally Recognized as Safe (GRAS). In Australia, the Australia New Zealand Food Standards Code did not list all food additives approved for use in Australia but instead stated the acceptability of additives listed in the GRAS lists of flavouring substances published by the Flavour and Extract Manufacturers' Association of the United States (which currently includes SLS). In Europe, SLS was listed in Annex II of Council Regulation (EEC) No 2377/90 meaning that no maximum residue limit (MRL) was required for a food product.
- The evaluator drew attention to the OECD SIDS Initial Assessment Report on Sodium Dodecyl Sulfate (1997) which concluded that, at present, SLS was of no concern for the general public and for workers. The evaluator also noted that the Cosmetic Ingredient Review of 1983 concluded that SLS appear to be safe in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with skin, concentrations should not exceed 1 per cent.
- The evaluator concluded the discussion of human safety by stating that the amounts of SLS used in cosmetics, and hence the potential human exposure, were significantly smaller than that used in animal studies. Consequently, considering the human health effects associated with SLS together with data indicating potentially extensive use in both industrial and consumer areas, it appeared that for consumers and workers, the human health hazards were low.

Product XXXXX

XXXXX.

Members also noted from the evaluation the following regarding exposure and risk for the product:

Exposure

- XXXXX.
- Based on the use pattern, direct contact with the product was considered to be low.
- The product was not intended for home/garden use. There was potential for exposure to product residues as a result of ingestion of meat from animals treated with the product.

Risk

- As exposure to the product was likely to be low, the risk was expected to be low. The only hazards of note were severe skin and eye irritation. Thus, as a precaution it was recommended that workers should wear gloves and goggles to protect themselves from accidental spillage when opening and using the product.
- There was no evidence that SLS was genotoxic (*in vitro* or *in vivo*), carcinogenic, or a reproductive or developmental toxicant. A NOEL of 116 mg/kg bw/day was identified from a rat 13-week oral toxicity study for increased serum alkaline phosphatase levels and relative liver weight

Members also noted in the evaluation report the following regarding hazard classification:

- SLS was not listed in Safe Work Australia's Hazardous Substances Information System (HSIS) Database (Safe Work Australia, 2009).
- With the available toxicology information, the evaluator has classified SLS as a hazardous substance according to the 2004 NOHSC *Approved Criteria for Classifying Hazardous Substances*, with the following risk phrases:

R21	Harmful in contact with skin
R22	Harmful if swallowed
R41	Risk of serious eye damage
R37/38	Irritating to respiratory system and skin

- The evaluator considered that the reported severity of the eye irritation reported in a published article and overseas review with concentrations up to 20 per cent SLS (i.e. it was not tested at 100 per cent as warranted by OECD Test Guideline 405: Acute Eye Irritation/Corrosion) justified the risk phrase R41 (Risk of serious eye damage) instead of R36 (Irritating to eyes).
- The evaluator applied the following generic cut-off concentrations for SLS:

Conc ≥ 25%	Xn: R20/21; R41-37/38
20% ≤ Conc < 25%	Xi: R41-37/38
10% ≤ Conc < 20%	Xi: R41
5% ≤ Conc < 10%	Xi: R36

[**NB:** R20 = Harmful by inhalation; R36 = Irritating to eyes

- The evaluator noted in an overseas review (Cosmetic Ingredient Review 1983) that 'moderate' eye irritation was reported 1 hour after administration of 2.5-5 per cent SLS, which was below the proposed 5 per cent cut-off concentration for hazard classification for ocular effects. The evaluator thought that consideration could be given to a specific concentration limit for eye irritation (i.e. < 5 per cent). However, as no quantitative information was provided on eye irritation scores over 72 hours and the evaluator had not seen or critically evaluated the primary study report, they considered that the above generic cut-off concentrations are presently appropriate.

XXXXX.

Pre-meeting Submissions

Pre-meeting submissions were received from:

XXXXX.

Members were advised that pre-meeting comments generally raised similar issues, including the following from the 12 industry submissions:

- Emphasised the wide range of products for human therapeutic, hygiene and cosmetic use.
- Scheduling of SLS in Australia would limit the manufacture and use of these products.
- Asserted that such a limitation was unjustified in view of its widespread continuous use throughout the world for a long period of time in low concentrations, without any significant reporting of adverse effects.
- Asserted that no other regulatory agency in the world restricted the use of SLS in the aforementioned products.
- The quoting of safety statements from such documents as 'NICNAS Existing Chemicals Report 9 October 2007 – Sodium Lauryl Sulphate' and 'Cosmetic Ingredient Review (1983)' was a common feature of the submissions.

Additionally, Members noted the following specific points from some individual submissions:

XXXXX

- The major uses of SLS was as a surface-active agent for emulsion polymerisation, in metal processing, detergents and shampoos; emulsifying, foaming, wetting, dispersing agent in creams, lotion and medical preparations; foaming, wetting, and dispersing agent in toothpaste, and emulsifier, whipping agent and surfactant in foods.
- SLS was also reportedly used as a cleansing agent in cosmetics; a whipping aid in dried egg products; food additive (emulsifier and thickener); emulsifier, wetting agent and adjuvant in insecticides.
- The risk to humans from SLS will depend on the amount of exposure to the chemical. The concentration of SLS used in cosmetics, and hence the potential human exposure, was significantly lower than that used in animal studies, especially in wash-off products.
- SLS meets the Schedule 6 criteria for skin irritation and eye irritation. The effects of SLS on the eye vary widely depending on the exposure. At 100 per cent corneal opacity, vacuolization, iritis and red swollen conjunctivae have been observed. Whereas at 2 per cent it was not irritating or only slightly irritating to the eyes. Although the hazards meet the Schedule 6 criteria it would be appropriate to

determine a concentration of SLS below which listing in Schedule 6 was not warranted. The additional skin and eye irritant tests in the OECD SIDS Initial Assessment Report 1995 were specifically suggested as starting points for determining cut-offs for leave-on and wash-off products, considering the studies have been conducted with varying concentration of SLS. Members noted the following from the OECD SIDS Initial Assessment Report 1995 (noting that some of these studies are from the 1940s and 1950s).

Test concentration	**Remarks**
Eye irritation studies	
10 per cent	One to 24 hours moderate irritant and at seven days mild irritant.
20 per cent	At 24 hour severe irritant and at seven days mild irritant.
5, 10 and 20 per cent	Irritant to highly irritant.
0.5, 1.0 and 2.0 per cent	Nil or slight irritant.
Skin irritation studies	
2 per cent	Score 5.2 *
10 per cent	Score 6.0*
20 per cent	Score 6.0 *

* - Maximum score index was 8.

XXXXX

- Provided the following table of concentrations of SLS in various products:

Product Type	Maximum concentration (% w/w
ARTG registered toothpaste	1.2
Cosmetics – Anti-dandruff shampoo	0.4
Cosmetics - toothpastes	2.0
Cosmetics – facial scrub	6.0

- Asserted that the toxicity of SLS appeared restricted to acute toxicity and skin and eye irritation which were observed at high doses in laboratory animal studies. It was argued that the concentrations of SLS in the products specified above did not constitute a human health hazard. Members noted that no data was submitted to support this argument.
- XXXXX submission drew the Committee's attention to:
  - Reiterated points discussed above from 'NICNAS Existing Chemicals Report 9 October 2007 – Sodium Lauryl Sulphate', the 'SIDS OECD Initial Assessment (1997)' and the 'Cosmetic Ingredient Review (1983)'.
  - 'Cancer Myths – Toothpaste (sodium lauryl sulphate) and cancer. WA Cancer Council, January 2008' - discusses the carcinogenicity of SLS and concludes that there was no evidence for carcinogenicity.
  - 'SLS – Qld Health Fact Sheet' – discussed issues of concern about SLS for the public. It concluded that the risk SLS presented to human health was related to the level of SLS in the product and how the product was used. In products containing relatively high levels of SLS, such as shampoo, prolonged exposure would not be expected to occur and skin irritation would be unlikely. In other

products such as toothpaste, the level of SLS was considerably lower, and although the membranes in the mouth and gastrointestinal tract would come in contact with low levels of SLS, the exposure would be transitory, and unlikely to cause irritation. As with any domestic product, if use of the product was thought to produce an adverse effect, such as irritation, continued use of that product would not be advisable.

XXXXX

- Submitted data on the uses and the usual concentrations for the use from the 'Handbook of Pharmaceutical Excipients' 4th ed.:

Use	Concentration (%)
Anionic emulsifier, forms self-emulsifying bases with fatty alcohols	0.5 – 2.5
Detergents in medicated shampoos	≈ 10
Skin cleanser in topical applications	1
Solubilizer in concentration greater than micelle concentration	>0.0025
Tablet lubricant	1.0 – 2.0
Wetting agent in dentifrices	1.0 – 2.0

XXXXX

- Noted that SLS was used at a range of concentrations. It was used in highest concentration in topical liquid dose forms like shampoos, skin washes and cleansers where its role was as a foaming agent or dispersant.
- While present in these formulations at high concentrations (between 10 to 30 per cent), these were typically wash-off formulations or were heavily diluted for skin contact use.
- In toothpastes SLS was present as a foaming agent typically at concentrations less than 5 per cent.
- SLS was used as an emulsifying and dispersing agent in creams and lotions at lower concentrations, typically less than 2 per cent.
- It was also used at low concentrations, less than 2 per cent, in solid dose forms, tablets and capsules as a lubricant to assist granule flow and prevent sticking to the punches during compression.

XXXXX

- Requested that the Committee note that SLS was listed in the EU as a cosmetics ingredient with cleansing, denaturing, emulsifying, foaming and surfactant functions without restrictions.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (a) toxicity and safety, (c) the potential hazards, (d) the extent and use patterns and (e) dosage and formulation.

A Member suggested that it was relatively straight forward to determine that SLS should have a Schedule 6 parent entry, based on the toxicological information provided. The Committee generally agreed that parent entry in Schedule 6 was appropriate for SLS given its potential for serious eye and skin irritation. There was some discussion as to whether this entry should be specific to SLS or whether it should be broadened to all lauryl sulphate salts, but Members generally agreed that the schedule entry should remain specific to SLS at this time.

The Committee then debated whether there should be exemptions to this general parent entry. It was noted, however, that there would be difficulties setting a low level cut-off because, while apparently justified by the extensive use of SLS at low concentrations without significant adverse events, the data provided appeared to be less robust with regard to setting a particular cut-off.

A Member suggested that perhaps this could be resolved by limiting the current consideration to the specific use pattern in the application, i.e. animal use using the proposed method of administration (7 per cent solution for intradermal injection). The Committee generally disagreed, however, as it now had data identifying a general risk from SLS and it would be inappropriate not to consider scheduling that responded to this potential risk.

A Member noted that the effects mentioned in the NICNAS review were concentration dependent and asserted that this, together with the long history of safe use at lower concentrations, should allow the Committee to arrive at some reasonably justifiable cut-offs for exemptions from scheduling. Members debated the appropriate concentration levels for the various uses of SLS, including wash off products, leave on cosmetics and other products, including toothpaste.

The Committee generally agreed that, based on the information tabled to date and taking a pragmatic approach that recognised the long history of safe use of many existing products, concentrations of ≤ 30 per cent for wash off products, ≤ 1 per cent for leave on products and ≤ 2 per cent for other products appeared appropriate for exemption from the Schedule 6 parent entry. There was some debate as to whether these cut-offs should specifically relate to cosmetic use. However, it was agreed that the risk largely related to concentration and whether it was a ‘leave on’, ‘rinse off’ or ‘other use’, regardless of whether or not it was a cosmetic.

A Member noted, however, that given the widespread use of SLS in many sectors, there was significant potential for unintended regulatory impact from this decision. The Committee agreed that it was appropriate to foreshadow the proposed SLS scheduling for consideration at the June 2010 meeting to allow time for additional public consultation, particularly with regard to the proposed cut-offs.

Members also discussed whether additional Appendix E standard statements or labelling criteria to qualify for the proposed exemptions were warranted. The Committee was of the view, however, that this was a debate best left for the June 2010 meeting as this needed to be informed by any additional arguments submitted in response to the foreshadowed scheduling of SLS.

RESOLUTION 2010/58 - 10

The Committee decided to foreshadow including sodium lauryl sulphate in Schedule 6 with exemptions for:

- wash-off preparations, containing ≤ 30 per cent sodium lauryl sulphate;
- in leave-on preparations containing ≤ 1 per cent sodium lauryl sulphate; or
- in other preparations containing ≤ 2 per cent of sodium lauryl sulphate.

The Committee also agreed to consider whether additional labelling requirements were warranted for SLS products at the June 2010 meeting.

Schedule 6 - New entry (foreshadowed decision for the June 2010 meeting)

SODIUM LAURYL SULPHATE **except:**

(a) in wash-off preparations containing 30 per cent or less of sodium lauryl sulphate;

(b) in leave-on preparations containing 1 per cent or less of sodium lauryl sulphate; or

(c) in other preparations containing 2 per cent or less of sodium lauryl sulfate.

6.8 SPINETORAM

PURPOSE

The Committee considered the scheduling of spinetoram.

BACKGROUND

Spinetoram is a cationic amphiphilic compound used for arthropod pest control. It is also known as a spinosoid, a synthetically modified spinosyn. Spinosyns are naturally derived fermentation products which are produced by the soil organism *Saccharopolyspora spinosa,* a novel bacterium of the order Actinomycetales. Spinetoram is prepared from a mixture of two natural spinosyns, spinosyns J and L. Structural analogues currently registered for similar purposes are spinosyns A and D (spinosad).

Spinetoram was included in Schedule 5 at the February 2008 meeting on the basis of its slight eye irritation and weak skin sensitisation.

DISCUSSION - SUBMISSIONS

XXXXX had prepared an evaluation report on an APVMA application by XXXXX seeking to change the scheduling and hazard classifications of spinetoram, the product XXXXX and a new formulation XXXXX. The evaluator recommended:

Public Health Standards

- The ADI for spinetoram was previously established at 0.06 mg/kg bw/day based on a NOEL of 6 mg/kg bw/day in a XXXXX day dietary study in XXXXX and using a 100-fold safety factor and this remains appropriate.
- Previously, no ARfD had been established for spinetoram because no data were submitted to enable an ARfD to be set; this remains the case.
- At its February 2008 meeting, the Committee created a new entry for spinetoram in Schedule 5. Based on the assessment of all the new submitted data, the evaluator considered the inclusion of spinetoram in Schedule 5 remained appropriate.

XXXXX.

Members recalled that an evaluation report on spinetoram was provided to the February 2008 meeting. Members were advised that this initial report incorrectly called the XXXXX product a skin irritant. This was subsequently corrected but was not referred back to the Committee at that time. Members also noted from the current evaluation report a comparison between the current and previous toxicological studies, including:

- In the current submission, the applicant has provided XXXXX new toxicological studies, including XXXXX acute toxicity studies, XXXXX genotoxicity studies and a XXXXX-month XXXXX dietary study for the active spinetoram; an eye irritation study for the product XXXXX, and XXXXX acute toxicity studies and XXXXX genotoxicity studies for the new formulation XXXXX.
- The evaluator indicated that all studies complied with contemporary international guidelines, and were relied on for risk assessment.
- Similar results were obtained in the current submission for studies on the active constituent spinetoram compared with the previous submission, with the exception of the skin sensitisation study by the XXXXX method. For the latter study, different conclusions were obtained from two independent tests which were conducted by the same laboratory. The previous test noted that the topical administration of XXXXX per cent, XXXXX per cent, and XXXXX per cent TGAC spinetoram elicited stimulation indices (SI) that were XXXXX-fold greater than the vehicle controls. The concentration that would cause a XXXXX-fold increase in proliferation was interpolated using the XXXXX per cent and XXXXX per cent responses and was calculated to be XXXXX per cent. The results were consistent with a weak dermal sensitisation potential of spinetoram as it elicited positive (SI > 3) lymphocyte

proliferation in XXXXX. However, a conclusion of non-skin sensitiser was reached for the new test.

- The main difference between the two sets of data was the composition of the test substance spinetoram. XXXXX. Both test mixtures fell within the composition range of spinetoram technical (50-95 per cent spinosyn-J and 50-5 per cent spinosyn-L).
- Since the different conclusions can not be simply attributed to the slight change in the proportion of two components XXXXX, the skin sensitisation potential of spinetoram TGAC could not be dismissed.
- In the XXXXX-day XXXXX dietary study, a NOEL of XXXXX was established based on aggregation of macrophages in the lymph notes, bone marrow and liver; vacuolization in follicle epithelial cells of thyroids observed at the next higher dose. The observations were similar to those in another XXXXX-day XXXXX dietary study XXXXX from the previous submission. In addition, these findings (aggregation of macrophages, histiocytes and mononuclear cells in lymph notes and other organs/tissues) are consistent with its potential of skin sensitisation revealed by XXXXX test.
- Consistent with the previous data, a new eye irritation study concluded that the product XXXXX is a slight eye irritant.
- The weak skin sensitising potential was shown only with the active constituent, but not for the two formulations. On the basis of skin sensitisation, a cut-off from Schedule 5 for 25 per cent or less of spinetoram would be appropriate. However, the two products caused slight eye irritancy in XXXXX (conjunctivitis and/or iritis) which resolved within 72 hours. Based on eye irritation, the products still fall within the guidelines for Schedule 5.

Toxicological findings from the evaluation report, including a number of findings from the previous evaluations, which remain unchanged, are summarised below:

TGAC

XXXXX.

- The acute toxicity studies of spinetoram in the XXXXX showed a low oral LD_{50} XXXXX, a low dermal LD_{50} XXXXX, and a low inhalational LC_{50} XXXXX. TGAC spinetoram was a slight irritant to the eye of XXXXX and did not irritate XXXXX skin. XXXXX for contact sensitisation indicated a weak sensitising potential or a non-sensitiser in different tests (discussed above).
- A comprehensive range of short term, subchronic and chronic studies in XXXXX were evaluated. There was no systemic toxicity in XXXXX administered spinetorum by dermal application at up to XXXXXX for XXXXX days. The most consistent observation in XXXXX was cytoplasmic vacuolation of parenchymal cells, epithelial cells, macrophages and fibroblasts in numerous organs. The effect was dose related in incidence and severity. Also noted were hyperplasia of the glandular mucosa of

stomach, multifocal degeneration and regeneration of skeletal muscle fibres and renal tubular epithelium, and increased splenic extramedullary haematopoiesis. XXXXX exposed orally in diet for XXXXX days at XXXXX showed extramedullary hematopoiesis of the spleen interpreted to be a response to the bone marrow necrosis and anaemia occurring at that dose.

- XXXXX.

- Spinetoram showed no evidence of *in vitro* or *in vivo* genotoxicity.
- Spinetoram is not a developmental toxicant in XXXXX.

Products

- The products are a XXXXX spinetoram (considered previously) and a new formulation containing XXXXX spinetoram.

XXXXX.

Members also noted from the previous 2008 evaluation report the following regarding exposure to the XXXXX product:

- XXXXX.
- The product is not intended for the home garden.
- Workers may be exposed to the product when opening containers, mixing/loading, and during application and cleaning up spills and equipment. The main route of exposure to the product dust or spray will be ocular or inhalation in the case of dust and dermal, inhalation or ocular in the case of the spray.
- Quantitative worker exposure estimates were deemed not necessary because of the low acute oral XXXXX, dermal XXXXX and inhalation toxicity XXXXX of the product and the observation that there is no evidence that the active constituent spinetoram is genotoxic, teratogenic or carcinogenic.

Members were advised that the occupational health and safety aspects of the new formulation XXXXX were currently under assessment XXXXX.

Members also noted the following regarding hazard classification:

- Spinetoram was classified as a hazardous substance in 2008 with the risk phrase R43 'May cause sensitisation by skin contact', using the *'Approved criteria for Classifying Hazardous Substances'* [NOHSC:1008 (2004)].
- This classification was re-affirmed in 2009 with a concentration cut-off of ≥ 1 per cent.
- XXXXX.

Pre-meeting Submission

XXXXX did not agree with the evaluation's recommendations on scheduling. The applicant argued that:

- The provision of updated data showed that spinetoram was not a skin sensitiser.
- Spinetoram was not a slight eye irritant using the scheduling criteria.
- Spinetoram does not meet either the criteria of NOHSC or of the GHS for eye irritation. Members noted that this appears to be the case.

The applicant argued that TGAC spinetoram and the two products currently do not meet any of the criteria that would require a Schedule 5 listing. The applicant understood that further debate could be had over the significance of the skin sensitisation aspect for TGAC spinetoram, given two different sets of results in XXXXX studies. Given the "tendency" for spinetoram at high concentrations to at least begin to elicit a proliferative response in the LLNA tests, the applicant indicated that it could still accept the Schedule 5 classification for spinetoram TGAC on the basis of skin sensitisation (although it still maintained that this low risk did not require scheduling). However, the applicant believed that concentration cut-offs were justified, at the least, for the products to be exempt from scheduling.

The applicant therefore recommended that spinetoram, if it is to remain in Schedule 5, be exempt from scheduling if the concentration is less than or equal to 25 per cent. The applicant noted that a precedent had already been established for the closely related analogue spinosad.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicology and safety and (c) potential hazards.

The Committee generally agreed that the skin sensitisation risk was low and probably did not require mitigation through scheduling. However, a number of Members remained concerned with regard to the eye irritancy potential of spinetoram.

Members debated the severity of the observed eye irritation and whether there was justification for a cut off from Schedule 5. A Member asserted that the eye irritancy was only slight, and, in the absence of other toxicity concerns, an exemption cut-off should be considered. Another Member also noted that an analogue of spinetoram was in Schedule 5 with a cut off at 25 per cent and suggested that this may be appropriate for spinetoram.

However, several Members noted that whilst the applicant argued for a cut off on the basis that there was no corneal damage observed, it was the persistency of the slight eye irritation that was the real concern that warranted inclusion in Schedule 5. Members also noted advice that the irritancy appeared to be an inherent property of the chemical rather than resulting from a particular formulation. A Member also asserted that eye irritation was observed with lower concentrations of spinetoram, and additionally the formulated

products appeared, from the data to date, to have the same irritancy profile as the active ingredient, and that there were no grounds for considering an exemption cut-off. The Committee agreed that the current entry for spinetoram in Schedule 5 remains appropriate.

RESOLUTION 2010/58 - 11

The Committee decided that the current scheduling for spinetoram remains appropriate i.e Schedule 5.

7. MATTERS REFERRED BY OFFICE OF CHEMICAL SAFETY (OCS) OR THE NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

7.1 LAURETH CARBOXYLIC ACID

PURPOSE

The Committee considered the scheduling of laureth carboxylic acid.

BACKGROUND

Laureth carboxylic acid (LCA) is the INCI name (International Nomenclature Cosmetic Ingredients) for a set of polymers containing, among others, polyethylene glycol-5 lauryl ether carboxylic acid (PEG-5 lauryl ether carboxylic acid) and PEG-6 lauryl ether carboxylic acid; also known as laureth-5 carboxylic acid and laureth-6 carboxylic acid respectively. LCA is a member of the alkylethercarboxylic acid class of chemical which in turn is a member of the anionic surfactant group of chemicals

LCA is used internationally as a surfactant and cleansing agent in a number of cosmetic and household products.

At the November 1999 meeting, the Committee noted the toxicity profile of a specific LCA salt, sodium laureth-6 carboxylate, in particular its severe eye irritancy potential, and agreed to list this specific LCA salt in Schedule 5 except for preparations containing ≤ 1 per cent.

DISCUSSION - SUBMISSIONS

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) prepared a review report on LCA following a notification from L'Oréal Australia. L'Oréal Australia indicated that LCA will be used as a surfactant or cleaning agent at ≤ 15 per cent in cosmetic and household products.

The report referred to a mixture of laureth-5 carboxylic acid and laureth-6 carboxylic acid under consideration as the 'notified chemical'. It was this mixture that was the test

substance used in the toxicological studies submitted, with published data being used to identify properties of the overall chemical class or similar chemical classes. The assessor recommended:

Public Health Standards

- When used in cosmetic and household products, the notified chemical is not considered to pose an unacceptable risk to public health if used at < 10 per cent with appropriate label statements regarding the potential for eye irritation. Members noted in a subsequent letter XXXXX recommended that Schedule 5 or 6 may be appropriate according to the concentration of LDA.

Occupational Health Standards

- The notified chemical is not considered to pose an unacceptable risk to the health of workers. However the following warning statements have been recommended:
  - Avoid contact with eyes.
  - Wear protective equipment.

Label statements

- Products should be labelled with a warning against eye contact, and directions on first aid measures if the product enters the eye (e.g. avoid contact with the eyes, in case of contact with eyes, rinse immediately with plenty of water and seek medical advice).

- The following warning statements have been recommended for products/mixtures containing the chemical:
  - Concentration ≥ 10 per cent: Risk of serious damage to eyes
  - Concentration 5 per cent ≤ concentration < 10 per cent: Irritating to eyes.

Members also noted the following from the assessment report:

- The data package contained studies on acute oral toxicity in rats, skin irritation in rabbits, eye irritation in rabbits, skin sensitisation in guinea pigs (maximisation test), bacterial mutagenicity and a bovine corneal opacity and permeability (BCOP) test.
- The notified chemical was referred for a consideration of scheduling based on the results of eye irritation tests.

Acute toxicity	
Rat oral LD_{50} (mg/kg bw)	>2000
Rat dermal LD_{50} (mg/kg bw)	No data
Rat inhalation 4-hr LC_{50} (mg/m^3)	No data
Skin irritation (rabbits)	Slightly irritating
Eye irritation (rabbits)	Severely irritating
Skin sensitization (Guinea pigs)	Non-sensitiser (maximization method)

Acute toxicity	
Mutagenicity – bacterial reverse mutation	Non-mutagenic

- Limited data was available to describe the likely toxicokinetic properties of the notified chemical. It has low molecular weight (< 500 Da.), is water soluble (in hot water), ionisable and has surfactant properties. It may therefore be absorbed to some degree across biological membranes. Oral absorption studies on alcohol ethoxylates (which have similar ethoxylated carbon chains) found that these chemicals were absorbed in the GI tract and extensively and rapidly excreted in the urine.
- Dermal absorption studies on alcohol ethoxylates found that significant amounts were absorbed through the skin of rats, but only small amounts (approximately 2 per cent) through the skin of human volunteers (although this was a small study). Although these chemicals do not contain the acid functionality of the notified chemical, it may be expected that it would act somewhat similarly and therefore may be absorbed to a small extent via the dermal route.
- The irritancy potential of the notified chemical was confirmed in a skin irritation test in rabbits. Very slight erythema was observed in all 3 animals from 60 minutes until 10 days after application. Peeling of the epithelial layer was observed in all 3 animals from days 9 to 12.
- The notified chemical (undiluted) was also found to be a severe irritant in an eye irritation test in rabbits, with corneal and iridial effects observed up to the end of the 20 day observation period. A bovine corneal opacity and permeability (BCOP) test was conducted on a product formulation containing the notified chemical at a concentration of < 15 per cent. The test substance was applied as a 10 per cent solution (therefore < 1.5 per cent the notified chemical). This diluted solution was found to be moderately irritating. Several members noted that this could potentially be used as a starting point in considering a figure for a low concentration exemption cut-off.
- The ICCVAM (Interagency Coordinating Committee on the Validation of Alternate Methods) recommended protocol for the BCOP states that surfactant-based preparations (e.g. product formulations) are usually tested neat, or can be diluted with justification of the selected dilution. In this case the test substance was a surfactant based preparation, but it was tested at 10 per cent dilution rather than neat and no justification for this dilution is given in the study report. The BCOP was currently accepted as a valid screening assay to determine severe irritants, but had not yet been validated for distinguishing between non, mild, moderate and severe irritants.
- The notified chemical did not contain any structural alerts for skin sensitisation and the notified chemical was found to be non-sensitising in a skin sensitisation (maximisation) test in guinea pigs.
- No repeated dose toxicity data were submitted for the notified chemical. Numerous repeat dose toxicity studies via the oral and dermal routes have been conducted in rats on alcohol ethoxylates (which have similar ethoxylated carbon chains). In these

studies, the effects observed were limited to changes in organ weights (with no histopathological changes) and hypertrophy of the liver (considered to be indicative of an adaptive response to metabolism rather than a toxic effect). Therefore the notified chemical may be expected to have similar effects after repeat exposure, but a quantitative determination of the repeat dose toxicity cannot be made.

- The notified chemical was found to be negative in a bacterial reverse mutation test at concentrations up to 2,500 μg/plate in the absence or presence of metabolic activation.
- No data is available on the *in vivo* genotoxicity or carcinogenicity of the notified chemical. There was no evidence of genotoxic or carcinogenic potential in studies on alcohol ethoxylates.
- Data as to the reproductive or developmental toxicity capacity of the notified chemical was not provided or discussed.

Members also noted the following regarding exposure and risk:

- The applicant has indicated that initially, the notified chemical will be imported as a component of finished cosmetic and household products (≤ 15 per cent). In future the notified chemical may be imported as an aqueous solution at 80-90 per cent for use as a raw ingredient.

Occupational health and safety

- Irritation was the primary risk presented by the notified chemical to workers in occupational settings. The notified chemical was found to be severely irritating to the eye of rabbits when applied undiluted. At a concentration of < 1.5 per cent the notified chemical was found to be moderately irritating to the eye in a BCOP test. The notified chemical was also found to be slightly irritating to the skin of rabbits when applied undiluted with evidence of inflammation persisting for > 10 days. Therefore, eye and to a lesser degree skin irritation, were potential risks to reformulation and/or transportation workers because of their handling of the chemical (80-90 per cent concentration) prior to and during reformulation. Appropriate handling techniques and the use of PPE (safety goggles, gloves, coveralls) should be in place to minimise any of these risks to workers during handling and reformulation. The implementation of these measures would ensure the likelihood of exposure was very low and the risk to workers would therefore not be considered unacceptable.
- Hairdressers and beauty therapists will encounter repeated dermal exposure to cosmetic products, such as shampoos, containing the notified chemical (≤ 15 per cent). The risk of eye exposure was not considered likely given the hairdresser would normally be standing up during application of the shampoo to a client who was expected to be seated. The notified chemical was slightly irritating to the skin when tested undiluted in rabbits. While it was unknown whether irritation was likely after exposure at ≤ 15 per cent it was assumed that significant irritation would be unlikely given the rinse-off nature of the products containing the chemical.

Public health

- Members of the public will experience widespread and frequent exposure to the notified chemical through daily use of cosmetic and household products (≤ 15 per cent) which will involve direct contact with the skin and hair. There was potential for accidental eye exposure while using shampoo products containing the chemical (≤ 15 per cent) and this could lead to eye irritation. This exposure could be either to the ≤ 15 per cent formulation, or to a diluted shampoo solution.
- The notified chemical was found to be severely irritating (with corneal effects) undiluted and moderately irritating to a diluted product formulation (<1.5 per cent notified chemical). As severe eye irritancy was observed with the undiluted chemical the potential for severe eye effects at concentrations greater than 10 per cent could not be ruled out. At concentrations < 10 per cent there was likely to be eye irritation, but this was less likely to be severe. Therefore, although the notified chemical may cause some eye irritation when used in cosmetic and household products the risk of serious eye damage may be minimised by restricting the concentration to <10 per cent and by clear and appropriate directions for use and safety precautions to avoid eye contact.
- First aid information should also be included on product packaging to minimise adverse effects if eye contact occurred. Extensive dermal exposure to the notified chemical in cosmetic and household products at ≤ 15 per cent was not considered to present an unreasonable risk of skin irritation given that the notified chemical was found to be only slightly irritating and was primarily intended for use in rinse-off products.
- A maximum systemic exposure of 0.79 mg/kg bw/day was estimated. As no repeat dose toxicity studies have been conducted, a NOAEL could not be established for the notified chemical. Therefore a quantitative risk assessment could not be conducted. However, given the expected low systemic toxicity after repeated use and the currently low introduction volume, the notified chemical was not expected to pose an unacceptable risk of systemic toxicity to the public when used in cosmetic and household products at ≤ 15 per cent.

Members additionally noted the hazard classification assigned to the notified chemical:

- The notified chemical was not listed in the HSIS database of hazardous substances. On the basis of the available data and using the 2004 NOHSC Approved Criteria for the Classifying Hazardous Substances, the assessor classified the notified chemical as hazardous with the following risk phrase: Xi; R41 Risk of serious eye damage.
- The assessor also classified the notified chemical using the GHS for the classification and labelling of substances as follows:

	Hazard category	***Hazard statement***
Serious eye damage	1 (irreversible effects on the	Danger: Causes serious eye damage Danger/Warning

	eye)	

- Members also noted that both APVMA and TGA have confirmed that LCA is not currently used in agvet or medicinal products.

Pre-meeting Submissions

XXXXX asserted that LCA was used safely as a surfactant in a number of cosmetic and home care products here and overseas without concern. XXXXX did not support the scheduling of this ingredient or its derivatives for use in personal and home care products. The submission also advised that Regulation (EC) No 1223/2009 of the European Parliament (November 2009) on cosmetic products does not list the notified chemical in any of its annexes. New Zealand, with its Cosmetic Products Group Standard 2009, takes up the European Union cosmetic amendments with the last update being 28 July 2009 and there were no restrictions on the notified chemical. The USA Cosmetics Ingredient Review Expert Panel has not reviewed the safety of the notified chemical nor have they listed it as a priority to do so.

XXXXX noted that LCA has been commonly used in low concentrations as a surfactant in cosmetic products for many years without any cause for concern. It was suggested that any consideration involving a schedule entry should exempt concentrations below an appropriate lower limit.

Additional issue

Members recalled that the November 1999 decision to list sodium laureth-6 carboxylate in Schedule 5, Appendix E and Appendix F was based on its severe eye irritancy potential. The data at that time showed that corneal opacity can persist for up to 11 days. Members also noted that at the November 1999 meeting:

- The Committee considered sodium laureth-6 carboxylate (22 per cent) related to a NICNAS Public Health Assessment Report.
- There was potential for widespread public exposure to the chemical in shampoo products, through the dermal route, and possibly from accidental ocular exposure.
- Apart from the severe eye irritant, the substance was also identified as a slight skin irritant, with effects reversed after 4 days.
- Based on the information provided on irritancy, the Committee decided an exemption cut-off for ≤ 1 per cent was appropriate.
- Members noted that the November 1999 Minutes do not indicate why Schedule 5 was considered appropriate for a severe eye irritant.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members generally agreed that the most relevant matters under Section 52(E)(1) were (a) toxicity and safety and (c) the potential hazards.

Members first considered the existing scheduling of sodium laureth-6 carboxylate (a sodium salt of a single specific LCA). Members considered if this specific entry remains appropriate in light of the new information tabled at this meeting, noting that if this specific entry were deleted then sodium laureth-6 carboxylate would then be captured by any general entry for LCA. The Committee agreed, however, that the current consideration should remain focused on the scheduling of LCA and that it did not wish to reconsider the existing scheduling of sodium laureth-6 carboxylate at this time.

Members then discussed whether the toxicity of LCA warranted a parent schedule entry, noting the similarity of concerns on this substance with those considered for sodium lauryl sulphate (item 6.7).

A Member suggested that according to the scheduling guidelines, a Schedule 6 parent entry would be appropriate for a substance that was clearly a severe eye irritant. Another Member argued, however, that the guidelines should be considered "on balance", i.e. that the complete toxicological profile be considered, noting both that there were no other significant toxicological concerns and the long history of use of LCA preparations without concern. Members generally agreed, however, that the long history of use was an argument more relevant to consideration of cut-offs or exemptions than for setting a parent entry. The Committee agreed that a parent entry in Schedule 6 was appropriate.

Members then discussed if an exemption or cut-off to Schedule 5 may be warranted. A Member asserted that if LCA was to be scheduled, Australia would be the only country in the world to do so. The Member noted that in this case there could be significant regulatory burdens as any required labelling on imported products would be uniquely Australian. The Member also reiterated that LCA was widely used with no history of adverse events. On this basis, the Member suggested that if scheduling was considered appropriate, an exemption cut-off of 15 per cent should apply.

Several Members remained concerned, however, by the potential for irritancy at 15 per cent, noting that the NICNAS report identified that severe eye irritation at concentrations > 10 per cent could not be ruled out. Additionally, Members noted that the NICNAS report also identified that preparations containing < 10 per cent were also likely to exhibit eye irritation (although less likely to be severe). A Member suggested, and the Committee generally agreed, that a Schedule 6 to Schedule 5 cut-off for 10 per cent or less was therefore appropriate.

Several Members continued to argue that there was sufficient information to also consider a low level exemption from scheduling. These Members asserted that, despite some deficiencies in the protocol for the irritation studies in the NICNAS report, it still provided reasonable support for considering that the irritancy potential of LCA, which

was significantly reduced at 1.5 per cent or less. The Committee generally agreed therefore to exempt preparations containing 1.5 per cent or less from scheduling.

A Member noted, however, given the widespread use of LCA in cleaning and cosmetic products, there was significant potential for unintended regulatory impact from this decision. The Committee therefore agreed to foreshadow the proposed LCA scheduling for consideration at the June 2010 meeting to allow time for additional public consultation, particularly with regard to the proposed cut-offs.

Members also discussed whether additional labelling was warranted (such as Appendix E entries). The Committee was of the view, however, that this was also best left to the June 2010 meeting as this needed to be informed by any additional arguments submitted in response to the foreshadowed scheduling of LCA.

RESOLUTION 2010/58 - 12

The Committee decided to include the laureth carboxylic acids in Schedule 6 with a cut-off to Schedule 5 for preparations containing ≤ 10 per cent laureth carboxylic acids, and a cut-off to unscheduled for products containing ≤ 1.5 per cent laureth carboxylic acid.

Schedule 5 – New entry (foreshadowed decision for the June 2010 meeting)

LAURETH CARBOXYLIC ACIDS in preparations containing 10 per cent or less of laureth carboxylic acid **except** in preparations containing 1.5 per cent or less of laureth carboxylic acid.

Schedule 6 – New entry (foreshadowed decision for the June 2010 meeting)

LAURETH CARBOXYLIC ACIDS **except:**

(a) when included in Schedule 5; or

(b) in preparations containing 1.5 or less laureth carboxylic acid.

8. OTHER MATTERS FOR CONSIDERATION

8.1 XXXXX

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

9.1 XXXXX

PHARMACEUTICALS

10. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCY(1)(c)

10.1 CHLORAMPHENICOL

PURPOSE

The Committee considered a post-meeting submission regarding the October 2009 decision to include chloramphenicol for ophthalmic use in Schedule 3.

BACKGROUND

Chloramphenicol is a bacteriostatic antibiotic with a broad spectrum of action against both Gram-positive and Gram-negative bacteria. Chloramphenicol has extensively been used in the topical treatment of ear and, in particular, eye infections, despite the fact that many of these infections are mild and self-limiting. It was also used topically in the treatment of skin infections. Acquired resistance has been reported.

At the February 2009 meeting, the Committee noted that the November 2008 New Zealand's Medicines Classification Committee (MCC) meeting was continuing its consideration of chloramphenicol, in particular the reclassification of eye preparations from prescription medicine to restricted medicine. Particular interest was paid to the possible development of resistance and to pharmacist training. It was concluded that, while there was insufficient information available to make a recommendation, the MCC would be open to reconsidering the request if addition supporting information was provided. Such information was subsequently submitted to the May 2009 MCC meeting, which in turn decided to allow chloramphenicol for ophthalmic use to be sold by a registered optometrist.

At the October 2009 meeting, the Committee decided to essentially harmonise with New Zealand by including chloramphenicol for ophthalmic use in Schedule 3.

DISCUSSION – SUBMISSIONS

Post-meeting Submission

XXXXX did not support the proposed rescheduling of chloramphenicol for ophthalmic use from Schedule 4 to Schedule 3. The following comments were made:

- No guidelines for the use of chloramphenicol by pharmacists existed in Australia, nor did pharmacy training cover the diagnosis of eye infections and appropriate referral for complicated cases. Asserted that it is inappropriate that the Committee allow

chloramphenicol to be accessed through a pharmacist without first ensuring the adequacy of pharmacy training.

- Did not support the statement that a pharmacist was equally suited to providing a diagnosis as a GP, due to the GP's training in diagnosis, treatment and management.
- Questioned that the Schedule 3 availability of chloramphenicol would lead to more effective treatment. Also questioned the pharmacists' abilities to distinguish between mild cases of bacterial conjunctivitis (from experience with the over the counter (OTC) supply of sulfacetamide and propamidine) from other serious causes of red eye e.g. the herpes virus.
- Pharmacists' discussions about the management and treatment of a condition with a patient might not be consistent, as research suggested that patients rarely received a consumer medicine information with their prescription or OTC medication (Vitry, A *et al* 2009, 'Provision of medicines information in Australian community pharmacies', *Pharmacy World & Science*, vol 31, n 2).
- Concerned that the rescheduling of chloramphenicol to OTC would affect concession card holders as they would no longer be entitled to the concession benefit.
- Also concerned about inappropriate use and the potential development of chloramphenicol resistance in the community.

May 2009 MCC minutes

Members noted the following from the May 2009 MCC meeting:

- The MCC discussed the need for correct diagnosis of eye conditions with several members asserting that best practise required the direct examination of the eye by a doctor or optometrist. Other members felt the training material provided would enable pharmacists to provide an accurate diagnosis. It was also noted that pharmacists had some experience with diagnosing and treating conjunctivitis.
- The MCC recommended that chloramphenicol for ophthalmic use be reclassified from a prescription medicine to a restricted medicine. It was further requested that this recommendation be delayed until training was provided to pharmacists and appropriate written information was available to be given to all patients purchasing the medicine.
- The NZ Pharmaceutical Society provided pharmacist training information.
- The training material listed conditions or symptoms needing referral to a GP. The MCC noted that pharmacists' awareness for referring all contact lens users could be improved and would be addressed in the training material. Further information for patients should be mandatory.
- The potential for resistance was discussed, with a member noting that chloramphenicol had been available OTC in the UK since 2005 and it had shown no overall increase in resistance.

October 2009 NDPSC minutes

Members noted the following discussions at the October 2009 meeting:

- A Member noted that the down-scheduling was a significant change that involved the availability of appropriate protocol for chloramphenicol to provide training to pharmacists. The Member suggested that it might therefore be more appropriate to wait for a full application to drive this consideration rather than rely on referral from the MCC. Members noted that it was not the role of the Committee to approve professional protocols.
- Several Members noted that key factor in considering the down-scheduling proposal was the relative abilities of pharmacist vs. GPs to diagnose eye infections. It was also noted that there were already OTC products available for 'acute red eye' provided by pharmacists. However, for accurate diagnosis of conjunctivitis a slit lamp was required, and GPs did not routinely have access to such equipment and therefore were no better at providing a diagnosing than a pharmacist. One Member argued that perhaps an optometrist would be better places to diagnose eye conditions in terms of available equipment. A Member asserted that, in making chloramphenicol for ophthalmic use available as Schedule 3, this would be allowing a relatively well qualified health professional to supply a substance with which they have had substantial experience. It was advised that chloramphenicol was currently being provided by nurse practitioners and other healthcare workers in remote communities through appropriate protocols.
- A Member drew the Committee's attention to the consequences of patients who might not be correctly diagnosed or referred to a GP when they should have been, with the most serious consequence being blindness. Several other Members contended, however, that while misdiagnosis may occur in a small percentage of cases, this was unlikely to differ significantly whether it was a pharmacist or a GP doing the diagnosis.
- A Member noted that since chloramphenicol became available OTC in the UK, there had been no reports of blindness. Another Member argued that pharmacists were qualified and capable of differentiating patients with simple eye infections from those needing to be referred, noting that pharmacists were already diagnosing patients and providing treatments with far less effective products.
- A Member noted that, if the Committee could satisfy itself that the benefits out weigh the risks then there should be no issues with including chloramphenicol for ophthalmic use in Schedule 3. A Member asserted that such conditions benefit from early detection and if an effective treatment was available OTC consumers would benefit.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits, (c) potential hazards, (f) the need for access, and (h) purpose for which a substance is to be used.

Several members asserted that the post-meeting submission reiterated arguments already considered at the October 2009 meeting rather than raising any substantially new concerns or issues. In particular, the post-meeting submission:

- Disputed the October 2009 conclusion that a GP was 'no better at providing a diagnosis than a pharmacist'. Several Members agreed, however, that the conclusions reached at the October 2009 meeting still applied, i.e. there appeared to be little, if any, significant difference between GPs and pharmacists in providing differential diagnosis between mild cases of bacterial or vial eye infection.
- Asserted that concession card holders would not be entitled to the concession benefit if chloramphenicol was available OTC. Members noted, however that a number of OTC products were currently available through the PBS and concluded that this argument was not correct.

Members generally agreed, therefore, that in the absence of substantial new information the decision of the October 2009 meeting remained appropriate.

RESOLUTION 2010/58 - 16

The Committee confirmed its October 2009 decision (resolution 2009/57-31) to include chloramphenicol for ophthalmic use in Schedule 3.

10.2 MIFEPRISTONE

PURPOSE

The Committee reconsidered the October 2009 mifepristone decision.

BACKGROUND

Mifepristone, commonly referred to as RU 486, is a synthetic steroid with an anti-progestational action as a result of competition with progesterone at the progesterone receptors. Doses of 1 mg / kg or greater have been shown to antagonise the endometrial and myometrial effects of progesterone. During pregnancy, it sensitises the myometrium to the contraction inducing action of prostaglandins. Mifepristone has been used, among other things, for medical termination of pregnancy.

Mifepristone also exhibits anti-glucocorticoid and weak anti-androgenic activity. Doses of 4.5 mg / kg or greater resulted in compensatory elevation of adrenocorticotropic hormone and cortisol. A number of potential uses for mifepristone beyond pregnancy

termination had been identified including the treatment of breast cancer, Cushing's syndrome, endometriosis, glaucoma, meningioma, ovarian cancer, prostate cancer and uterine fibroids.

At the June 2006 meeting, the Committee deferred a recommendation from the Trans-Tasman Harmonisation Working Party to harmonise mifepristone to a future meeting (at the time mifepristone was unscheduled in Australia and was a prescription medicine in New Zealand).

At the October 2009 meeting, the Committee created a new entry for mifepristone in Schedule 4. The Committee also agreed to impose additional controls through inclusion of mifepristone under Appendix D, paragraph 1 and paragraph 3.

While mifepristone was not currently approved for marketing in Australia, provisions in the *Therapeutic Goods Act 1989* (the Act) and associated regulations allow the Secretary of the Department of Health and Ageing to authorise a medical practitioner to prescribe it as an unapproved therapeutic good.

DISCUSSION - SUBMISSIONS

Members were advised that a proposal to set-aside the Appendix D, paragraph 1 entry arising from the October 2009 decision had been put forward. The proposal raised the following concerns:

- Appendix D, paragraph 1 appeared, historically, to have been applied to enable the states and territories to apply additional controls on the prescribing of particular products already approved for marketing in Australia.
- Appendix D, paragraph 1 had not previously been used in relation to unapproved therapeutic goods. It was argued that this was largely because there were already provisions in the Act and associated regulations allowing the TGA to authorise individual medical practitioners to prescribe unapproved therapeutic goods. These provisions, known as the Special Access Scheme (SAS), allow two general types of access:
  - Category A, which does not require prior approval of the TGA; and
  - Category B (and Section 19(5)), which requires prior approval of the TGA, with strict conditions.
- Appendix D, paragraph 3 allowed the Committee to further restrict the access through the SAS to Category B only.
- It was argued that given the SAS provisions, Appendix D, paragraph 1 was redundant until such time as a product was approved for marketing in Australia. To impose Appendix D, both paragraph 1 and paragraph 3 when there was no approved product might be needlessly duplicative.

- It was therefore proposed that, since there was no mifepristone product currently approved for marketing in Australia, only an Appendix D, paragraph 3 listing was necessary at this time. It would therefore be appropriate to considered setting-aside the Appendix D, paragraph 1 mifepristone listing from the October 2009 decision.

October 2009 meeting

Members also recalled the following from the October 2009 minutes:

Scheduling application

- Mifepristone appeared to fulfil the criteria for a Schedule 4 medicine both in terms of the indications for its use and the characteristics of the substance itself. The indications for which it would normally be prescribed (termination of pregnancy and related obstetric conditions as well as treatment of inoperable meningiomas) were all conditions which would require the intervention of a medical practitioner for diagnosis and management.
- Mifepristone could have significant undesirable effects, many of which were related to its pharmacological action (uterine cramping and contractions, vaginal bleeding) and use was not recommended in patients with renal or hepatic failure. The drug was also considered unsafe in patients with porphyria. Mifepristone was metabolised via cytochrome P450 3A4 and there was potential for interaction with both inducers and inhibitors of this hepatic enzyme system.
- Although no products were included on the ARTG, there were a number of provisions in Therapeutic Goods legislation allowing access to unapproved medicines. It would therefore be preferable that mifepristone be considered for scheduling. This would provide certainty with respect to controls of access throughout the jurisdictions.

Pre-meeting submissions

- A number of submissions strongly expressed views opposing the availability of mifepristone for the indication of medical termination.
- Several other submissions supported the proposal to specifically list mifepristone in Schedule 4. These submissions also agreed that inclusion in Appendix D was appropriate to limit its prescribing to suitable qualified medical practitioners.
- One submission, while supporting a Schedule 4 listing with appropriate restrictions, requested that the Committee consider the need for access to mifepristone for the treatment of serious medical conditions aside from medical termination. The submission highlighted that in the US, restrictions were imposed on use such that only a licensed provider for the termination of pregnancy could use/prescribe the drug. The restriction automatically precluded all oncologists and cancer specialists or other specialists from using mifepristone to treat cancers and other serious medical conditions.

Member's discussion

- Members acknowledged that there was strong opposition to medical termination of pregnancy by some members of the public. However, Members agreed that it was important to clarify that the matter before the Committee was a proposal to consider appropriate scheduling for mifepristone (which was currently unscheduled). It was not the Committee's role to approve the Australian use of mifepristone products. Product approval was an entirely separate matter subject to a regulatory process through the TGA.
- A Member advised that there had been no application submitted to the TGA to register mifepristone in Australia, nor was it currently approved for marketing in Australia. However, there were arrangements in place to make unapproved products such as mifepristone available via the TGA's SAS. However, with mifepristone being unscheduled at this time, there was a degree of uncertainty with respect to uniformity. Members generally agreed, in order to provide clarity for jurisdictions and because the substance patently had properties and uses warranting some degree of restriction or control, that it was appropriate to consider scheduling mifepristone.
- Several Members argued that in addition to a Schedule 4 entry there was a need to consider additional controls through Appendix D. The Committee generally agreed that it would be appropriate to restrict the current access to unapproved mifepristone products to healthcare professionals authorised by the Secretary of the Commonwealth Department of Health and Ageing (Appendix D, paragraph 3). Other Members agreed that an Appendix D, paragraph 3 listing was particularly appropriate as this would no longer allow potential access to unapproved mifepristone products through Category A of the SAS (which did not require prior approval of the TGA) i.e. access would only be allowed for those categories of the SAS which require prior approval of the TGA, with strict conditions (either Category B or Section 19(5)).
- One Member asserted, however, that Appendix D, paragraph 3, while largely picked up, was not adopted in all jurisdictions. To cover such circumstances the Committee agreed that access to mifepristone should also be limited to only be from, or on the prescription or order of a medical practitioner authorised to do so by the state / territory jurisdictions i.e. Appendix D, paragraph 1.
- A Member additionally suggested that, due to the nature of conditions that mifepristone had been used for; mifepristone access should additionally be limited to only from, or on the prescription or order of a specialist. Other Members opposed restricting access to specialists in a particular field, noting that in the US mifepristone supply was restricted to specialists in gynaecology and obstetrics and as a consequence mifepristone access was withheld for oncologists or other specialists who may desire access to treat patients with cancer or another serious illness. Additionally, a Member noted that in some remote areas in Australia there were communities that did not have access to specialists and medical care was limited to general practitioners. Members agreed that prior authorisation through Appendix D, paragraphs 1 and 3, together with the Schedule 4 listing, were sufficient controls and there was no need to additionally restrict access to specialists in a particular field.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (d) extent and patterns of use, and (i) other matters that the Committee considers necessary to protect public health.

Members first discussed whether the October 2009 decision to include mifepristone in Appendix D, paragraph 1 had been premature given the absence of any product approved for marketing in Australia.

A Member asserted that an Appendix D, paragraph 1 listing was redundant in relation to controlling access to mifepristone in the current circumstances i.e. the only access would be through those provisions in the Act and associated regulations by which the TGA can authorise a medical practitioner to prescribe an unauthorised therapeutic good (i.e. compliant with the controls and restrictions set out for SAS and Section 19(5), including approval by an ethics committee). Historically Appendix D, paragraph 1 was used as a means of applying additional restrictions for medicines after they have been approved for marketing and were therefore no longer subject to these specific TGA controls.

The Committee generally agreed that the important matter was that mifepristone remained Schedule 4 (rather than, as was the case prior to the October 2009 decision, unscheduled). The Committee also agreed that, in light of the historical use of Appendix D, paragraph 1 and that the controls under this paragraph were redundant given the existing TGA controls on accessing unapproved medicines, it was appropriate to set aside the October 2009 decision to include mifepristone in Appendix D, paragraph 1. A number of Members also argued, and the Committee agreed, that an Appendix D, paragraph 1 entry could be reconsidered if and when a mifepristone product were approved for marketing.

A number of Members then queried whether there remained a need for the October 2009 Appendix D, paragraph 3 entry. Members recalled that the October 2009 meeting had agreed that it was appropriate that, in addition to a Schedule 4 listing, access to mifepristone should be restricted to suitable qualified medical practitioners authorised by the Secretary of the Commonwealth Department of Health and Ageing. While this restriction was in place already for access through SAS Category B and Section 19(5) of the Act, Members remained concern that there may be potential for access through SAS Category A (which did not require prior approval of the TGA).

A Member noted, however, that SAS Category A access was restricted to patients defined as “persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment”. Several Members argued, therefore, that the October 2009 concern over Category A access was largely overstated, as its use in routine medical termination would not be grounds for such access. A Member additionally noted that there were strict Customs controls, including the need for a permit, on the importation of mifepristone.

In light of this clarification, a number of Members asserted that the current SAS arrangements were adequate, noting the conditions in place for access under Section 19(5). The Committee agreed that it would be redundant to list mifepristone in Appendix D, paragraph 3 and therefore agreed that it was appropriate to also set aside the October 2009 decision to include mifepristone in Appendix D, paragraph 3.

RESOLUTION 2010/58 - 17

The Committee decided to vary the October 2009 resolution (2009/57 – 24) by setting aside the mifepristone entries in Appendix D, paragraph 1 and paragraph 3.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

11.1 MONTELUKAST

PURPOSE

The Committee considered a request for a correction to the October 2009 minutes regarding montelukast.

BACKGROUND

At the October 2009 meeting, the Committee considered a proposal to down-schedule montelukast 10 mg, for the symptomatic treatment of seasonal allergic rhinitis, in Schedule 3. The Committee agreed that the risk versus benefit ratio was not strong enough, in light of a number of concerns, and rejected the proposal.

DISCUSSION

XXXXX had asserted that a statement relating to a USFDA black boxing warning, in the October 2009 Record or Reasons, was incorrect. The USFDA has not required a black box warning in the US prescribing information (PI) for montelukast. Therefore, it was requested that a correction be recorded to this effect. Member's noted that the applicant's assertion was correct in that no such black box warning had been issued by the USFDA.

Members also noted that:

- The October 2009 Record of Reasons for montelukast records the statement "Several Members noted with concern the association of montelukast with reported neuropsychiatric events in children. These associations had been of concern to, and evaluated by the USFDA with a consequential increase to the warning requirements i.e. a black box warning in the US PI."
- The applicant argued that the USFDA request pertained to the inclusion of a precaution in the drug prescribing information. The USFDA published this request on its website in June 2009 with the clause "Neuropsychiatric events have been

reported in some patients taking montelukast, safirlukast and zileuton. FDA has requested that manufacturers included a precaution in the drug prescribing information."

- The applicant asserted that the updates to the 'precaution' section was incorporated in the montelukast US PI and subsequently approved by the FDA in August 2009.

XXXXX.

RESOLUTION 2010/58 - 18

The Committee agreed to record as a corrigendum to the October 2009 minutes that the USFDA did not require a black box waring in the US PI for montelukast.

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

12.1 SUSDP, PART 4

12.1.1 FLURBIPROFEN

PURPOSE

The Committee considered the scheduling of flurbiprofen.

BACKGROUND

Flurbiprofen is a propionic derivative non-steroidal anti-inflammatory drug (NSAID), which is structurally related to ibuprofen. It possesses analgesic and anti-inflammatory properties and has been in therapeutic use for over 20 years.

Flurbiprofen was included in Schedule 4 in November 1993. The Committee rescheduled flurbiprofen in divided preparations for topical oral use containing 10 mg or less of flurbiprofen per dosage unit from Schedule 4 to Schedule 3 in February 2000. The subsequent rescheduling to Schedule 2 for this type of preparation was agreed at the October 2002 meeting. The Committee's decision was based on post-marketing safety data demonstrating that the preparation had a very low potential for causing adverse effects and no evidence of abuse or misuse.

In Australia, current flurbiprofen products available include lozenges for treatment of sore throats (Schedule 2) and eye drops for treatment of intraoperative miosis (Schedule 4).

DISCUSSION - SUBMISSIONS

An application from XXXXX requested an exemption from scheduling for flurbiprofen when for topical oral use. The following options were proposed by the applicant:

Option 1:

Schedule 4

- FLURBIPROFEN **except** in preparations for topical oral use and not labelled for the treatment of children 12 years of age or less.

Option 2

Schedule 4

- FLURBIPROFEN **except** in preparations for topical oral use and not labelled for the treatment of children 12 years of age or less:

    (a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit; or

    (b) in undivided preparations containing 0.25 per cent w / v or less or 10 mg or less per dose of flurbiprofen.

The applicant particularly noted that it was seeking to include undivided formulations (currently Schedule 2 flurbiprofen was restricted to divided preparations) in its requested exemption as it was wishing to XXXXX.

The applicant's arguments in support of an exemption for flurbiprofen for topical oral use were summarised as follows:

- The current Schedule 2 access had been in place for over 7 years with no instances of misuse or abuse recorded.
- Self-management with an NSAID-containing product would be preferable to treating an acute sore throat with prescription antibiotics.
- Systemic analgesics such as paracetamol or NSAIDs were effective treatments when used regularly.
- Post-marketing experience of flurbiprofen OTC in Australia / NZ since 1999 was favourable.
- XXXXX.
- The availability of flurbiprofen for oral topical use exempt from scheduling would be particularly important for communities in rural remote areas and would provide an alternative to systemic NSAIDs.

Lozenge

- Flurbiprofen at a dose of 8.75 mg in a lozenge formulation had been shown to be effective in relieving the symptoms of sore throat.
- A lozenge formulation acts locally on the pharyngeal mucosa with little or no systemic side effects.

- The use of the low dose present in each lozenge, the low maximum daily dose recommended and the low overall dose contained in a packet of lozenges suggested that there was little likelihood of systemic adverse effects.

Mouthwash and Spray

- The use of a mouthwash or a throat spray preparation similarly would be very unlikely to lead to systemic adverse effects.
- XXXXX.

Evaluation Report

The evaluation supported a flurbiprofen exemption from scheduling for oral topical use and recommended the applicant's Option 2 as it set an upper limit for the concentration for undivided preparations. Members particularly noted the following summary of the evaluator's reasons for this recommendation:

- Flurbiprofen is a NSAID which had been assessed as effective in the symptomatic treatment of sore throat when applied topically in the form of throat lozenges at a dose (8.75 mg, up to 8 times a day), much lower than the recommended daily systemic anti-inflammatory dose (150 – 300 mg).
- Flurbiprofen, when administered topically to the buccal mucosa, had a low systemic bioavailability and reaches very low plasma concentrations because of the low unit dose. It had a very low to absent potential for abuse, drug interactions, or masking of serious disease states.
- Flurbiprofen for topical oral use (symptomatic relief of sore throat) was suitable for self-identification and treatment without professional advice.
- Use of flurbiprofen lozenges in Australia and NZ had been associated with an excellent safety profile, and there was no expectation that a shift from Schedule 2 to exempt would result in any additional problems.
- There was extensive marketing experience within Australia and overseas XXXXX. The spontaneous reporting rate of adverse events (AE) has been very low, and post-marketing surveillance suggested that the lozenge formulation was very safe in OTC use. There was no reason to expect that a shift to general availability would be associated with any significant change in the safety profile.
- The applicant provided evidence to support its assertions, and taken together this constituted a reasonable argument in favour of an exemption.
- The evaluator concluded that the application had demonstrated that the indication and the products were suitable for self-identification and self-treatment without professional advice, and that the safety profile indicated that there would not be any significant risk to consumers during self-management of sore throat.

The evaluation also addressed the following concerns:

- The public health-related argument that the unscheduled availability of flurbiprofen for topical use would reduce inappropriate prescribing of antibiotics was not well supported. However, it was reasonable to argue that the topical use of a NSAID was likely to be more effective than some of the other oral antibacterial throat lozenges, and safer than systemic use of a NSAID.
- XXXXX.
- The comparison in a study in XXXXX, between flurbiprofen lozenges 8.75 mg (a systemically inactive dose) and aspirin 500 mg (a systemically active dose) was an inappropriate one, and made interpretation of the safety comparison difficult.

Members additionally noted the following from the evaluation:

- There were no particular public health considerations in relation to the exemption of flurbiprofen lozenges. The flurbiprofen lozenges were packaged in blister packs to reduce the risk of childhood poisoning.

Potential for abuse

- Misuse of lozenges was very unlikely. The low dose (10 mg or less) per unit and short half-life result in a very low risk of interactions with other drugs, masking of treatment of other disease states, or bioaccumulation.
- There was only a low potential for harm from inappropriate use as the mean systemic bioavailability of flurbiprofen after buccal treatment relative to oral systemic administration was 10 per cent or less. Plasma concentrations after use of any of these proposed products would be expected to be very low.
- XXXXX included a warning against using more than eight lozenges in a day, but even if the entire pack of 16 were consumed in one day the total dose would be 140 mg and therefore not likely to cause harm.

Toxicity and safety

- The dose of flurbiprofen in each dosage unit was low in comparison with its usual oral dose used when a systemic antiinflammatory effect was required (150 – 300 mg). Plasma concentrations after use of oral preparations would be expected to be very low.
- The safety of topical oral flurbiprofen was supported by data from clinical trials and pharmacovigilance from XXXXX.
- The evaluator agreed that the topical oral use of flurbiprofen was safer than systemic ingestion of NSAIDs paracetamol, aspirin or ibuprofen for treating sore throat.

Adverse Events

- The low dose present in each lozenge, the low maximum daily dose recommended (70 mg) and the total dose contained in a packet of lozenges (140 mg in a pack of 16 lozenges; 210 mg in a pack of 24) compared with the usual daily dose of oral

flurbiprofen (150 – 300 mg) suggested that there was little likelihood of systemic adverse effects during use of the lozenges.

- The use of a mouthwash XXXXX or the throat spray XXXXX similarly would be very unlikely to lead to systemic adverse effects.
- Data was available up to and including December 2008. There were XXXXX serious adverse events in XXXXX patients. Most effects occurred in a single patient, and there were no signals to suggest a causative relationship.
- The applicant's argument that a shift from oral systemic ibuprofen to oral topical flurbiprofen for treatment of sore throat would result in a reduction in the risk of systemic adverse effects was reasonable.

Post-marketing experience

- Lozenge preparations had been approved as a non-prescription medicine in the UK, Thailand, Poland, Australia, New Zealand, Italy, Hong Kong, Slovakia and Ireland. XXXXX very few suspected adverse drug reactions (ADRs) had been reported and none of the reported serious AEs had been attributed to flurbiprofen treatment.
- Mouthwash and oral throat spray preparations have only been registered in Italy, and the experience with these formulations was very limited. However, it was reasonable to extrapolate safety from the lozenge formulation, given that mouthwash and oral throat spray bioavailability was lower.
- XXXXX examining the safety of flurbiprofen in the lozenge formulation compared with soluble aspirin in patients with sore throat concluded that flurbiprofen lozenges (8.75 mg) did not differ from aspirin (500 mg) in terms of serious AEs with the exception of AE related to the taste of the product. As previously mentioned, the interpretation of this safety comparison was difficult, in addition, the XXXXX included the involvement of the pharmacist in taking a medical history and confirming whether or not flurbiprofen was a suitable treatment. This procedure was more in keeping with Schedule 3 use than unscheduled use.
- Overall, flurbiprofen lozenges (8.75 mg) had a good safety profile and it could be inferred from XXXXX that over XXXXX per cent of consumers were able to accurately choose flurbiprofen as a suitable treatment for their sore throat without assistance, supporting exemption from scheduling.

Food or drug interaction

- At the dosage used in the lozenge preparation, flurbiprofen was very unlikely to have significant interactions with other drugs or foods that would require counselling.

Therapeutic index

- This issue was not directly addressed in the submission. The therapeutic index of an NSAID was difficult to assess, given their propensity to cause ADRs in susceptible patients at the dose required to have a systemic anti-inflammatory effect.

- In relation to topical oral use, it appeared that the therapeutic local effect occurred at much lower doses than were required for the systemic effect, and the therapeutic index was thus substantially higher for this indication and preparation than for oral dosage forms.

Risk of masking a serious disease

- Given the indications and low dose of flurbiprofen present in lozenges, the risk of masking a serious disease was likely to be very low. The risk was further reduced by the instructions to use the preparations for no longer than 3 days. XXXXX there were four episodes of quinsy throat infection in participants in the flurbiprofen group, and in all cases subjects ceased taking the lozenges and sought further medical opinion.
- Additionally, given the low plasma concentrations reached after administration of topical oral flurbiprofen, the risk of compromising medical management was very low.

Purposes

- The indication for use, sore throat, was an ailment or symptom that:
  - does not require ongoing or close medical diagnosis or management;
  - is easily recognised by the consumer;
  - is amenable to short term treatment; or
  - is capable of being monitored and self managed by the consumer, without requiring advice and counselling.
- XXXXX.

Comment on the Evaluation Report

The applicant provided a response to the evaluation report. Members particularly noted the following arguments:

- In addition to some minor errata, the applicant asserted the following regarding the proposed labelling:
  - XXXXX.

Pre-meeting Submissions

XXXXX disagreed with the proposal on the basis that:

- Flurbiprofen, being a NSAID, had the potential to cause harm to patients with cardiovascular, renal and gastrointestinal conditions. Furthermore, it was a Category C medicine in pregnancy ‘drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible’.

XXXXX further asserted that:

- Lozenges and medications for the treatment of sore throat generally, were regarded by the public as benign and with little potential to do harm. The majority of the general public were unaware that ingredients contained in throat lozenges were absorbed into, and could have systemic effects on, the body.
- The potential risk of these proposals outweighed any possible benefits.
- It would not be opposed to extending the existing Schedule 2 entry for flurbiprofen to allow an undivided preparation to be marketed as a Schedule 2 medicine.

XXXXX also disagreed with the proposed exemption for oral topical flurbiprofen. It concluded that there was neither a public need for increased access to topical oral preparations nor that unrestricted access to such products was in the public interest. It was also concerned with the contraindication for these products during the third trimester of pregnancy and possible interactions with commonly used medicines. In addition, comments with particular reference to section 52E were provided:

(b) Risks and Benefits

Contraindications

- The Prescribing Information (PI) from MIMS for flurbiprofen lozenges indicated that these products were contraindicated where there was a hypersensitivity to, or history of, asthma, bronchospasm, rhinitis and urticaria related to aspirin or other NSAIDs. Flurbiprofen was also contraindicated for people with a history of peptic ulceration and during the third trimester of pregnancy.

Interactions

- The PI advised that although no clinical evidence exists for the interaction between OTC flurbiprofen and anti-hypertensives such as angiotensin-converting enzyme inhibitors and beta-blockers, it still advised caution when using this combination.
- Also listed was interference with anticoagulant therapy and a recommendation to avoid concomitant use with methotrexate therapy.

(c) Potential Hazards

- The PI listed the third trimester of pregnancy as a contraindication due to the increased risk of premature closure of the foetal ductus arteriosus in utero and persistent pulmonary hypertension of the newborn infant.
- It was inappropriate to rely on label warnings to caution the use of flurbiprofen in pregnancy as it had been recognised that public health literacy was a significant issue and people did not always read and following the directions or warnings contained on or within the packet.

- For a long time, the public have had access to unrestricted topical oral products such as Butter Menthols® which could be consumed in large quantities without any significant safety concern.
- Contended that the public generally regard preparations such as unrestricted lozenges as being without risk and may ignore pack warnings or dosage instructions.

(f) Need for Access

- Did not support that there was a demonstrated need for increased access to topical oral flurbiprofen products.
- Alternatives such as Strepsils Plus® are available without restriction from the same range of topical oral products which were indicated for minor mouth and throat infections and symptoms of inflammation. Strepsils Plus® contains 10 mg lignocaine and lignocaine had a Category A listing for use in pregnancy 'drugs which have been taken by a large number or pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect effects on the fetus having been observed'.
- Therefore a safer, and still effective product, was already available without restriction.

(h) Purposes

- Severe sore throat symptoms required intervention of a health professional to evaluate whether it could be a more serious condition.
- If topical oral flurbiprofen was exempted from scheduling, people with more serious conditions may be further delayed in having health professional intervention which could lead to greater complications.
- XXXXX emphasised that consideration of any changes to topical oral preparations must not inadvertently capture eye preparations containing flurbiprofen. The current Schedule 4 listing for flurbiprofen eye products was appropriate.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (b) risks and benefits, (e) dosage and formulation and (f) need for access.

Members first discussed the applicant's proposed restriction against OTC flurbiprofen use by children 12 years of age or less. A Member noted that no information or argument on this issue was presented by the applicant. Currently, there was no such scheduling restriction. Additionally, Members noted that current OTC flurbiprofen products registered on the Australian Register of Therapeutic Goods did not appear to include a restricted indication for use in children. Members agreed that, should a scheduling amendment for OTC flurbiprofen be agreed to at this meeting it should not include a

restriction against use by children at this time, as this was best addressed by the regulator given the lack of tabled data on this issue.

Members then discussed whether there were sufficient grounds for exempting all flurbiprofen for topical oral use as requested. In particular:

- A Member noted that flurbiprofen lozenges had been available in Australia as a Schedule 2 medicine since 2002, and that there had been few reports of AEs or systemic toxicity. The Member argued that flurbiprofen lozenges (10 mg or less per dosage unit) would be a safer alternative than ibuprofen (or other NSAID) tablets for managing sore throat symptoms, noting that the majority of people self-medicate for relieving these symptoms. Another Member contended, however, that this benefit would only be tenuous and any real benefit of flurbiprofen lozenges over NSAID tablets could not be quantified from the information tabled.
- A Member asserted that the objections to exempting certain flurbiprofen preparations from scheduling in a number of pre-meeting submissions did not take account of the risk mitigation resulting from the very low doses proposed (both for divided and undivided preparations). A Member recalled, however, that the Committee, in considering several potential toxicity concerns from the use of NSAIDs at past meetings, had noted that while toxicity was largely dose-related, there were idiosyncratic reactions to NSAIDs.
- Several Members were concerned that there was a risk that unscheduled flurbiprofen lozenges could be perceived as 'lollies' rather than as a medicine, particularly by children. These Members noted that this was not as significant an issue for tablets as the community had generally retained the perception that unscheduled tablets were still medicines and were usually more alert to heeding labels on tablets, especially regarding use while pregnant.
- A Member disagreed with the above concern and argued that there were company developed public education campaigns to emphasise the presence of active compounds in lozenges. The Member also asserted that the lolly argument was unsubstantiated and, in any case, the risk of harm was quite low and a product presentation would still need to be approved by the regulator. Another Member contended, however, that it was entirely intuitive for children to see lozenges as lollies, and that in fact, this was a major reason that companies felt the need to develop education campaigns in the first place. The Member also asserted that this may have been a reason for the applicant's proposed restriction against OTC flurbiprofen use by children 12 years of age or less, as discussed above.
- A Member also noted the argument that an exemption from scheduling would facilitate access for communities in rural / remote areas in Australia with limited access to a pharmacy. However, Members agreed that this argument had little basis as jurisdictions had arrangements in place which allowed the supply of Schedule 2 products outside pharmacies in such circumstances.

- A Member reiterated that flurbiprofen had been classified as a Category C pregnancy risk. A number of Members asserted that products in this category should not be available unscheduled.
- Several Members asserted that a better case needed to be made regarding the public health benefits of unscheduled flurbiprofen. These Members contended that the applicant did not provide convincing data to support the need for unscheduled flurbiprofen for topical oral use, noting that there were alternatives already available.

Members generally felt that the case for unscheduled access to topical oral flurbiprofen had not been made. These Members agreed that there was only a small risk, but this needed to be balanced against little benefit. The Committee agreed that preparations of flurbiprofen for topical oral use (10 mg or less) should remain in Schedule 2.

Members then discussed the issue of whether all topical oral use formulations of flurbiprofen should have consistent scheduling (currently only certain divided preparations qualify for the Schedule 2 entry). A number of concerns were raised, including:

- A Member argued that while there was a reasonable degree of post-marketing experience with OTC lozenges in Australia, a similar claim could not be made regarding the undivided preparations. The Member suggested that this may be grounds for maintaining the current restriction of only allowing certain divided preparations to be Schedule 2.
- A Member also noted that the indication for use was not consistent among the different formulations. While the indication for flurbiprofen lozenges was for the relief of sore throat symptoms, the indication for mouthwash and spray, such as were available in Italy, appeared to be for conditions such as pharyngitis, stomatitis and gingivitis. However, the Member did not see that this was necessarily a reason for not allowing Schedule 2 access to low concentration undivided flurbiprofen formulations.
- A Member queried whether there may be concern that children could ingest a larger flurbiprofen dose from a mouthwash product compared to the current OTC divided preparations. Another Member asserted, however, that this risk could sufficiently be mitigated by setting a low concentration cut-off (such as the proposed 0.25 per cent) which, even if the whole contents were ingested, would mean that the total flurbiprofen dose would still be too low to cause systemic toxicity.

Members generally agreed that there was sufficient information to support rescheduling low concentration undivided flurbiprofen formulations, when for topical oral use, in line with the current Schedule 2 scheduling of some divided preparations. Members also agreed that the Schedule 4 to Schedule 2 cut-off for these preparations should be 0.25 per cent or less, or 10 mg or less per dose.

A Member reiterated that this scheduling decision did not equate with a marketing approval for such products – any such approval of an OTC undivided flurbiprofen product would be a matter for the TGA.

RESOLUTION 2010/58 - 19

The Committee decided:

- That divided preparations for topical oral use containing 10 mg or less per dosage unit remained appropriately scheduled in Schedule 2.
- To broaden the Schedule 2 flurbiprofen entry to include undivided preparations containing 0.25 per cent or less or 10 mg or less per dose of flurbiprofen.

Schedule 2 – Amendment

FLURBIPROFEN – Amend entry to read:

FLURBIPROFEN in preparations for topical oral use when:

(a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit; or

(b) in undivided preparations containing 0.25 per cent or less, or 10 mg or less per dose, of flurbiprofen.

12.1.2 NICOTINE

PURPOSE

The Committee considered the scheduling of nicotine.

BACKGROUND

Nicotine is an alkaloid found in the nightshade family of plants (*Solanaceae*) which constitutes approximately 0.6–3.0 per cent of dry weight of tobacco, with biosynthesis taking place in the roots, and accumulating in the leaves.

The first-line pharmacological intervention for nicotine dependence from cigarette smoking is nicotine replacement therapy (NRT) for reducing the cravings associated with smoking cessation - available as chewing gum, transdermal patches, inhalers, nasal sprays, sublingual tablets, and lozenges. Combination therapy with different types of NRT has also been tried as a means of increasing efficacy.

In June 1991, the Schedule 4 entry for nicotine was amended to include all preparations (except Schedule 3 chewing tablets) which could be used as an aid in smoking cessation, containing between 2 and 4 mg of nicotine or roll-on devices with 0.65 per cent or less of nicotine e.g. transdermal patches.

At the August 1993 meeting, the Committee rejected a proposal to have 2 mg sublingual tablets rescheduled from Schedule 3 to Schedule 2 and 4 mg sublingual tablets rescheduled from Schedule 4 to Schedule 3.

At the November 1993 meeting, the Committee agreed that Schedule 4 remained appropriate for patch formulations. Subsequently, at the November 1997 meeting, transdermal patches were included in Schedule 3.

Nicotine 2 mg chewing tablet was rescheduled to Schedule 2 in February 1997. However, in deciding to reschedule the 4 mg tablet from Schedule 4, the Committee decided that this higher dosage should remain as Schedule 3 to facilitate the counselling of heavy smokers by a pharmacist.

Inclusion of nicotine gum and transdermal patches in Appendix H was agreed at the August 1998 meeting.

At the February 1999 meeting, the Committee amended the Schedule 3 nicotine entry to 'Nicotine as an aid in withdrawal from tobacco smoking in preparations for inhalation or sublingual use.'. At the August 2001 meeting, the Committee agreed that nicotine lozenges would have a comparable safety profile to that of sublingual tablets, and so it was appropriate to also include lozenges in Schedule 3. Subsequently, lozenge preparations were down scheduled to Schedule 2 in June 2003.

Down scheduling of nicotine in cartridges for oral inhalation to Schedule 3 and inclusion in Appendix H was decided at the November 1998 meeting. Subsequently, nicotine inhalers were rescheduled from Schedule 3 to Schedule 2 in February 2002. The decision was made on the basis that nicotine inhaler had a safety and side-effect profile consistent with other NRT products including the chewing gum.

At the October 2003 meeting, the Committee agreed to exempt nicotine in gums, transdermal patches and lozenges from the requirements of scheduling to harmonise with New Zealand. The Committee was of the view that widening the availability of NRT products should encourage more smokers to quit smoking and, as a first step, this approach should improve public health outcomes. This decision was confirmed at the February 2004 meeting following consideration of post-meeting comments. The Committee agreed to delete nicotine from Schedule 3 and it was later deleted from Appendix H in June 2004.

At the June 2005 meeting, the Committee agreed, in the interests of harmonisation with New Zealand, to exempt sublingual tablets from scheduling. The current nicotine entries therefore exempt chewing gum, lozenges, or preparations for sublingual or transdermal use.

DISCUSSION - SUBMISSIONS

Members were advised that new data and a set of new references were included in the applicant's response to the evaluation report. The Committee settled its position on this issue prior to engaging on the rest of this consideration. Members noted that the applicant was informed when invited to respond to the evaluator's report that inclusion of new data could result in deferral should the Committee consider that this data requires evaluation. The applicant advised that:

- The new data was in response to the evaluator's comment (see below) that no objective efficacy or safety data to support oromucosal nicotine spray (ONS) equivalence with orally-administered NRT was provided in the application.
- This new information was provided to emphasise that adequate data was available to demonstrating the safety and efficacy of ONS.
- The ONS was used as an example to highlight the inconsistent approach depending on the route of administration i.e. buccal versus sublingual would be scheduled differently, regardless of safety and efficacy.
- For clarification, the application was not a request for scheduling consideration of ONS, but rather for the consideration of a consistent approach to scheduling of buccal vs. sublingual preparations.

Members noted that in this case it eventuated that it was possible to forward these new data to the evaluator prior to the meeting. The evaluator was able to provide comment (see below). As the evaluator had seen, and commented on the new data, Members agreed that, in this particular case, there was no need to defer the consideration.

Applicant's Submission

XXXXX requested an amendment to the current exemptions for NRT. The proposal was that this exemption be broadened to buccal preparations in general, rather than the currently specified buccal dosage formats i.e. chewing gum and lozenges. XXXXX. The following wording was proposed for the exemption 'for use as an aid in withdrawal from tobacco smoking in preparations for buccal, sublingual or transdermal use'.

Members noted the following summary of the applicant's arguments:

- NRT formats were currently available over-the-counter (OTC) as chewing gum, lozenge and inhaler (absorbed via the buccal mucosa), patch (transdermal) and microtab (sublingual).
- Preparations for sublingual or transdermal use were currently scheduled the same, and not differentiated by the specific dosage format.
- Buccal preparations and sublingual preparations had comparable safety and efficacy, hence the argument for grouping buccal preparations seemed reasonable given this principle was already applied to sublingual format.

- When administered in a pharmaceutical formulation, nicotine was practically devoid of the serious long-term adverse health consequences of smoking tobacco.
- There was only a low risk of NRT masking a serious disease or compromising medical management of a disease.
- The Committee had previously considered matters under 52E regarding NRT and asserted that the principle had already been established that certain NRT products might safely be sold unscheduled and did not require a pharmacist to supervise the sale.
- ONS products are sprayed directly into the mouth (rather than specifically under the tongue), making the route of administration buccal. As a result ONS currently falls under Schedule 4.
- The plasma levels following a single-dose of ONS XXXXX were within the range of those for marketed buccal preparations such as nicotine 2 mg and 4 mg chewing gum and nicotine 2 mg and 4 mg lozenge.
- Studies demonstrated that nicotine from ONS administered via buccal (oral transmucosal) or sublingual routes would produce the desired efficacy, with no incidents or trends indicating that the adverse event profile of ONS might differ significantly from buccal preparations.

Evaluation Report

The evaluator recommended approval of the proposal to exempt ONS products, pending supportive, objective, evidence of safety and efficacy of ONS, noting that such evidence was not in the application. Should such data be provided and an exemption be contemplated for buccal preparations, then for greater clarity, the evaluator suggested the following wording "for use as an aid in withdrawal from tobacco smoking in preparations for oromucosal or transdermal absorption".

The evaluator assessed the application against 52E, and Members particularly noted the following:

(a) Toxicity and Safety, ***(b) Risks and Benefits*** and ***(c) Potential Hazards***

- The key issue in determining whether ONS should be exempt was evidence that this method of administration was as efficacious and as safe as nicotine delivered sublingually or via chewing gums and lozenges. However, no objective evidence was provided.
- The relevant studies referred to by the applicant were not cited. Only two references of indirect relevance were provided: one which indicated that the similarity in pharmacokinetic profiles between nicotine chewing gum and lozenges (Beradi, RR *et al*, 2006, 'Handbook of Nonprescription Drugs and Interactive Approach to Self-Care, 15th Ed, Chapter 50), and another between nicotine chewing gum and sublingual

tablets (Mollander, L and Lunell, E, 2001, 'Pharmacokinetic investigation of a nicotine sublingual tablet.', *Eur J Clin Pharmacol*, vol 56, pp 813-9).

(d) Extent and Patterns of Use

- Although no data were provided in the application, it was generally well-known that NRT use was common.
- It was unclear how the exemption of nicotine in all preparations for buccal absorption would impact on the extent and pattern of use of NRT.

(e) Dosage and Formulation

- The applicant did not discuss this matter in detail. However, of relevance was the statement about plasma levels achieved with ONS being comparable with those of existing, orally-administered NRT products.

(f) Need for Access

- The applicant did not specifically discuss the need for access to ONS. It would be beneficial to have evidence that currently available NRT products were not suitable for some patients, or that some patients prefer ONS preparation.

(g) Potential for Abuse

- There appeared to be little potential for abuse of currently available NRT products. Without detailed information about doses to be used in ONS, no firm conclusions could be drawn about its abuse potential.

(h) Purposes for which a Substance is to be used

- The use of ONS would be the same as for currently available NRT products.

Applicant's Response to the Evaluation Report

The applicant provided a response to the evaluation, which was summarised below:

Oromucosal nicotine spray (ONS)

- ONS would be an NRT product with a fast onset of effect in combination with consumer sensory acceptance.
- A compliance study was discussed which showed a higher rate of intrapersonal preferences for using ONS preparations than NRT previously used by the subjects.

Safety and Efficacy

- The main difference between ONS and other oral forms of NRT was the speed of absorption. The applicant asserted that XXXXX, and also asserted that ONS PK profile relating to the extent of absorption was similar to other already approved oral NRT products.
- XXXXX.
- No ONS studies on clinical efficacy had been finalized by the time of this application.

- Although ONS was not bioequivalent to any existing NRT product, plasma levels were comparable to those achieved with available NRT. It was reasonable to argue that efficacy of ONS was covered by the lower strength 2 mg product benchmarks and the systemic safety was covered by the upper benchmark provided by the corresponding 4 mg products.
- XXXXX. It was asserted that these show that treatment-related AEs were transient and generally well tolerated and similar to AEs seen for gums and lozenges preparation.
- Safety studies were noted which contained data from XXXXX subjects in PK studies and XXXXX subjects from a XXXXX use study. Based on these data, it had been concluded that ONS was well tolerated and the speed of absorption did not seem to cause a safety issue.
- Most regular smokers were adept at self-regulation of their nicotine intake, maintaining their plasma nicotine levels within a narrow range, so it was unlikely that use of ONS would result in elevated plasma nicotine levels.

Adverse Events (AEs)

- The applicant stated that safety of nicotine from NRT was well described in the literature.
- XXXXX, chewing gum and lozenges preparations were used as reference product. A total of XXXXX treatment-related AEs were reported, of which XXXXX related to the use of ONS XXXXX.

Misuse

- Asserted that ONS labelling with dosage recommendations would minimise the risk of misuse or long-term use. The applicant considered the use of ONS XXXXX to meet the criterion of having a low abuse potential.
- Also advised that the safety profile of the ONS would be kept under appropriate review, however, given the well characterised safety profile of NRT used in smoking cessation no future safety issues were anticipated.

Biopharmaceutics

- Study reports have shown that the absorption of nicotine from ONS XXXXX was fast with the plasma level having increased significantly compared to baseline already at the first sampling time point XXXXX after administration.
- XXXXX confirmed that the absorption of nicotine from ONS XXXXX was more rapid than that from gum and also showed superiority versus lozenge. Plasma levels over the first XXXXX after administration were significantly higher for ONS than for gum and lozenge, even when comparing a XXXXX of ONS with 4 mg doses of gum and lozenge. The maximum concentration was generally reached XXXXX with ONS as compared with 45 minutes with lozenge and 30 minutes with gum.

- XXXXX.

Efficacy

- Based on literature, all approved NRT (gum, transdermal patch, inhaler, lozenges and sublingual tablets) could increase the rate of quitting by 50-70 per cent, regardless of setting.

Evaluators Comment on Applicant's Response

The evaluator was able to go through the applicant's response prior to the meeting. The evaluator concluded that the new data were not convincing to support the applicant's assertion on comparable efficacy and safety between ONS and existing oral NRT preparations.

Pre-meeting Submissions

XXXXX were not opposed to the proposal to replace the specific exemptions for chewing gum and lozenge dosage forms with a more general 'buccal preparations' exemption from scheduling.

XXXXX support for the proposal included:

- Current oral formats were limited to gum, lozenge and sublingual products which were required to be in the mouth for up to 30 minutes. Convenient, faster dissolving alternatives than lozenges and sublingual preparations that are easier to use than gum, could help improve compliance with smokers' plan to quit smoking. Some people were not able to use gums because of oral care problems.
- Extending the current nicotine scheduling exemption may enable easy access to alternative NRT formats that were faster dissolving than a lozenge and easier to use than a gum.

Safety

- The experience with NRT over 20 years of use demonstrated that it had a favourable safety profile with few significant untoward effects, even in those individuals with cardiovascular disease.
- Nicotine in lozenges and gum formats were well-tolerated. The exposure to nicotine with other buccal forms was likely to be the same as those associated with the lozenge and / or gum.
- There were few risks associated with oral (buccal) formats of NRT.

XXXXX also asserted that based on an anatomical approach, it seemed reasonable to broaden the current exemption to 'buccal preparations', as nicotine dosage forms for NRT, with the exception of patches for transdermal use, were all administered via the buccal cavity and absorbed through the buccal mucosa. Noted that the nicotine in chewing gums and lozenges was quickly absorbed through the buccal mucosa, with only

a small quantity being swallowed; the nicotine in inhalers also delivered nicotine in vapour which was absorbed via the mucosa in the mouth and throat.

XXXXX also sought confirmation that the existing Schedule 2 entry for preparations for inhalation would remain. Members noted, however, that this was not necessarily the case. A broadening to 'buccal' could also exempt other buccal products, i.e. mouthwashes or similar. Members also noted that the ARTG listed the route of administration of NRT inhalers as 'buccal'. This might result in potential conflict within the current Schedule 2 entry for inhalation NRT.

XXXXX additionally noted that while the change in wording was appropriate, it sought clarification on whether:

- A definition for "buccal preparations" will be included under Part 1 ('Interpretation').
- Would other existing entries specifying 'lozenges' be affected. Was the intention for lozenges to be captured under 'buccal preparation' for all substances?

XXXXX also provided additional comments, including:

- Concern on how the proposed change would impact products regarded as 'partial' buccal preparations, such as lozenges. Noted that in the full product information for some nicotine lozenge preparations, it appeared that absorption was through the buccal mucosa and oral ingestion.
- Noted that clarification on the definition and extent of buccal absorption may be required.
- It would seem that the use of NRT for reasons other than smoking cessation, such as for temporary abstinence or reducing the number of cigarettes smoked, was fairly common. This was of concern because the exemption of NRT from scheduling was to support smoking cessation in an effort to improve population and individual health outcomes. The beneficial effect of temporary abstinence or reduction in smoking was questionable.
- Noted that XXXXX had consistently held the view that NRT supply for smoking cessation was best managed under the care of a health professional who had the capacity to assess and monitor individual requirements. Asserted that professional intervention enhanced patient outcomes and was more cost-effective for the consumer. Questioned whether exemption of NRT from scheduling had resulted in increased and sustained smoking cessation.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (d) extent and pattern of use, (e) dosage and formulation and (h) purpose for which a substance is to be used.

Members noted that buccal preparations included chewing gum, lozenges, sublingual and oromucosal sprays but could potentially included other formulations as well. A Member suggested that potential adoption of a broad exemption for all buccal preparations may therefore require a definition of 'buccal' as it could be interchangeably used with other types of oral mucosal preparations such as sublingual. Other Members argued, however, that buccal was reasonably understood. The Committee generally agreed that, as there had been no real issues with regard to those current schedule entries which used buccal, this issue need only be pursued if there was a decision to include 'buccal' in any exemptions arising from the current consideration (which was not the case as discussed below).

Members then discussed whether there were grounds for broadening the current nicotine exemptions for specific NRT uses to all buccal preparations. A Member argued that it would not be an issue to extend the current NRT exemptions to allow for new, innovative formats, such as, for example, ONS. Another Member also asserted that there was potential benefit in encouraging new options for unscheduled NRT, particularly for those few who were unable to chew, maintain a lozenge in the mouth or maintain a patch on the skin. Several Members, however, felt that an exemption for all buccal preparations would be too broad and could potentially see it expand to less suitable formats such as mouthwashes and toothpastes. The Member also noted that such a broad exemption appeared potentially incompatible with maintaining the scheduling of nicotine inhalers in Schedule 2. The Committee generally agreed that specific exemption would be more appropriate.

Members then discussed whether sufficient evidence had been tabled to support any specific additions to the current NRT exemptions. Members generally agreed that the only potential addition at this time, for which data had been presented, was a specific exemption for ONS. A Member asserted, however, that as there were currently no ONS products approved for marketing in Australia, there was no experience with the preparation OTC and therefore it may be premature to consider an exemption. Other Members noted that an exemption from scheduling was not a marketing approval and that a case would still need to be made to the regulator. A Member was also concerned regarding the consequences if a person, particularly a child, ingested a dose of liquid containing nicotine from a spray format. Another Member asserted, however, that both the systemic availability of nicotine and the concentration of nicotine in a spray would be low, which would reduce any risk of unwanted systemic effects. The Committee agreed to extend the current nicotine exemptions to also include preparations for oromucosal spray use.

Members confirmed that the exemption for oromucosal spray use was not intended to exempt the current Schedule 2 NRT inhalers.

RESOLUTION 2010/58 - 20

The Committee decided to amend the scheduling of nicotine to exempt oromucosal spray use, as an aid in withdrawal from tobacco smoking, from scheduling.

Schedule 4 – Amendment

NICOTINE **–** Amend entry to read:

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

(a) when included in Schedule 2; or

(b) for use as an aid in withdrawal from tobacco smoking in chewing gum, lozenges, or preparations for sublingual, transdermal or oromucosal spray use.

12.1.3 PARACETAMOL COMBINED WITH PHENYLEPHRINE AND GUAIPHENESIN

PURPOSE

The Committee considered the scheduling of paracetamol combined with phenylephrine and guaiphenesin.

BACKGROUND

Paracetamol+phenylephrine combination

Paracetamol combined with phenylephrine was exempted from scheduling in June 2007. The Committee decided that the safety profile of these substances was such that allowing a fixed combination to be unscheduled was reasonable. The Committee also felt that there was sufficient Australian market experience to support its decision.

Currently, paracetamol+phenylephrine+guaiphenesin combination (PPGC) products are available as Schedule 2.

Paracetamol is only partially harmonised with NZ. Australia restricts the exemption to those preparations where the only therapeutically active constituent is paracetamol (other than phenylephrine or when combined with effervescent agents), while NZ does not have such a restriction.

Phenylephrine

Phenylephrine hydrochloride is a sympathomimetic amine with effects on adrenergic receptors. Its pressor activity is weaker than that of noradrenaline but of longer duration. After injection it produces peripheral vasoconstriction and increased arterial pressure, and it also causes reflex bradycardia. It reduces blood flow to the skin and to the kidneys. Phenylephrine and its salts are most commonly used for the relief of nasal congestion.

They are frequently included in preparations intended for the relief of cough and cold symptoms.

At the October 2005 meeting, the Committee considered the scheduling of phenylephrine with a view to harmonising with NZ. The NZ Medicines Classification Committee (MCC) recommended that phenylephrine for oral use should be a general sale medicine in products containing 50 mg or less per recommended daily dose. Subsequently, at the February 2006 meeting, the Committee confirmed such a scheduling amendment for phenylephrine.

Guaiphenesin

Guaiphenesin is an expectorant. It was indicated to help loosen phlegm and thin bronchial secretions.

Guaiphenesin was first scheduled in February 1967 as a Schedule 4 substance under the entry 'mephenesin and its derivatives'. At the February 1968 meeting, the Committee decided to separate guaiphenesin from mephenesin. The Committee also considered use in small doses as an anti-tussive agent, and decided to include guaiphenesin in preparations containing 120 mg or less in Schedule 3.

Liquid preparations containing 2 per cent or less of guaiphenesin were included in Schedule 3 in November 1978. Subsequently, at the November 1984 meeting, both the divided and liquid preparations of guaiphenesin were rescheduled to Schedule 2.

At the February 1998 meeting, the Committee agreed to exempt guaiphenesin in oral preparations from Schedule 2 when accompanied by a statement warning against use in children under two years of age.

As a result of harmonisation between Australia and NZ, the Committee decided at the May 2001 meeting to delete the Schedule 2 entry and amend the Schedule 4 entry to exempt divided preparations containing 200 mg or less of guaiphenesin and oral liquid preparations containing 2 per cent or less of guaiphenesin (current entry).

Guaiphenesin 1200 mg or less in modified release (MR) preparations was scheduled in Schedule 2 in February 2009 (confirmed at the June 2009 meeting). At the May 2009 MCC meeting, MR preparations of guaiphenesin (maximum daily dose of 2400 mg), when in pack sizes of 5 days supply, were exempt from scheduling, and in pack sizes of not more than 30 days supply, were down-scheduled to Schedule 3 in NZ. At the October 2009 meeting, the Committee decided to not harmonise with the NZ decision. The Committee felt that, as yet, there was limited Schedule 2 experience in Australia with the MR formulations.

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXX requested an extension to the current scheduling exemption for paracetamol+phenylephrine combinations to also include guaiphenesin. The applicant's arguments in support of the requested exemption included:

- Current unscheduled combination products containing paracetamol+phenylephrine did not provide chest cough relief. Guaiphenesin had been shown to have clinical utility in the management of coughs. Therefore a purchase of at least two products was currently required.
- Certain paracetamol+phenylephrine combinations, and qualifying guaiphenesin single active preparations were already exempt from scheduling. It was argued that it was a logical step to have a PPGC product available as an unscheduled preparation.
- PPGC products were classified as general sales in the UK and NZ.
- The combination did not diminish the established safety and efficacy of the individual active ingredients while each exerted a therapeutic benefit at its normal dose and dosage interval.
- Asserted that there was a need for greater accessibility to more options of medications available for self-medication in remote areas. Also argued that an unscheduled combination was appropriate to facilitate the access by consumers, including:
  - Acceptance of coughs and colds as being suitable for self-care treatment.
  - The long OTC history of the use of paracetamol, phenylephrine and guaiphenesin in Australia.
  - Low risks and high benefits of these products for treating cold and flu symptoms.
  - Offered greater accessibility.
  - Paracetamol, phenylephrine and guaiphenesin were not known to cause sedation and hence the combination was not expected to have the potential to cause sedation.
  - No potential for abuse / misuse of the combination was shown from post marketing data. Additionally, the proposed small pack size did not encourage inappropriate prolonged use.
  - No concerns for safety for the PPGC were shown from UK, PSUR, ADRAC and NZ post marketing data.
  - Overall, approximately XXXXX subjects had been exposed to PPGC products to date and the number of adverse reports totalled XXXXX. The incidence of adverse events was estimated to be very low.

Information on the pharmacokinetics (PK) profile, therapeutic dose and recommended dosing of paracetamol, phenylephrine and guaiphenesin were also included in the application. Overall, the following assertions were made:

- Paracetamol is readily absorbed, mainly from the small intestine (the systemic availability varies between 70 to 90 per cent). It is rapidly and widely distributed throughout the body and is eliminated from plasma with a half-life of approximately 2 hours.
- Phenylephrine is irregularly absorbed from the gastrointestinal (GI) tract and undergoes first-pass metabolism by monoamine oxidase in the gut and liver; orally administered phenylephrine thus has reduced bioavailability.
- Guaiphenesin is rapidly absorbed after oral administration. It is also rapidly metabolised by oxidation.
- Noted that the PK of the active ingredients can be said to be comparable and their bioavailability from both the powder and the capsule were not expected to differ.

The applicant also addressed matters under section 52E, as outlined below under the Evaluation Report section.

Evaluation Report

The evaluator supported the requested exemption. In the evaluator's opinion, the applicant appropriately argued a need for greater access to more options for cost-effective self-medication, particularly in rural regions where there could be limited access to pharmacies. A summary of the evaluator's reasons for this recommendation was provided:

- Given that paracetamol+phenylephrine combination preparations and guaiphenesin single ingredient preparations were all currently unscheduled, a combination product of all three ingredients could potentially save patients with cold and flu symptoms accompanied with chesty cough, to have to buy more than one product.
- The incidence of adverse events for the PPGC was not expected to be higher than what was observed for the paracetamol+phenylephrine combination and guaiphenesin as a single ingredient. The small pack sizes for the proposed products would also limit to some extent the inappropriate long-term use or potential for prolonged delays before seeking medical attention when the symptoms persist.

The evaluator also agreed that the following arguments from the application were generally appropriate:

- Paracetamol, phenylephrine and guaiphenesin were not known to cause sedation and hence the combination of the three substances was not expected to have potential to cause sedation.
- Pharmacovigilance / post marketing data to date showed no concerns for safety for the combination product containing paracetamol, phenylephrine and guaiphenesin.

- PPGC would provide a cost-effective treatment option, not previously available unscheduled.
- Low risks and high benefits of the proposed products for treating cold and flu symptoms in which coughs were common.
- Pharmacovigilance data from Australia had shown that the paracetamol+phenylephrine combination, when used at the recommended doses (unscheduled medicine), was associated with few adverse reaction reports.
- Guaiphenesin as an unscheduled medicine was also shown to be safe.
- Pharmacovigilance / post marketing data showed low potential for abuse / misuse of the combination product.

The evaluator was concerned, however, that the application did not discuss risks mitigation of ingestion of PPGC powder (to be served dissolved as a hot lemon drink) by children 12 years of age or less. Compared to a capsule formulation, there was a higher risk that a sachet preparation, once dissolved, may be inadvertently administered in children of 12 years or less, particularly if PPGC was exempted and the product became more accessible.

The evaluator further assessed the application against matters under 52E, and Members particularly noted the following:

(a) Toxicity and Safety

- The applicant presented median LD_{50} findings from published safety data for paracetamol, phenylephrine and guaiphenesin. The safety of phenylephrine and guaiphenesin were compared to that of paracetamol, which the applicant claims were well documented and supported. The safety margin of phenylephrine and guaiphenesin were relatively wide compared to paracetamol.

	LD_{50}	**Maximum recommended daily dose**	**LD_{50} / daily dose**
Paracetamol	2404 mg/kg (rat)	57.1 mg /kg (4 g)	42
Phenylephrine hydrochloride	350 mg/kg (rat)	0.7 mg/kg (48.8 mg)	500
Guaiphenesin	1540 mg/kg (rat)	11.4 mg/kg (800 mg)	135

- Noted that the applicant's claim that, overall, PPGC products were safe to use in lactating women, appeared to be appropriate.
- Paracetamol and guaiphenesin were both Category A pregnancy medicines 'drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed'.

- Phenylephrine was Category B2 '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'.
- XXXXX.

(b) Risks and Benefits

- The evaluator noted the applicant's table summarising risks and benefits of paracetamol, phenylephrine and guaiphenesin in the treatment of common colds (below) and made the following comments:

	Benefits	**Risks**
Paracetamol	Effective at providing symptomatic relief of sore throat and fever. It is the preferred analgesic of choice as it has fewer side effects. It can be used when aspirin and ibuprofen are contraindicated.	Accidental overdose possible: marketed in many different preparations and in combination products. Drug-disease precaution: chronic liver disease. Drug-drug precautions: warfarin.
Phenylephrine	Decrease subjective symptoms and nasal airways resistance.	Drug disease precautions: diabetes, heart disease, hypertension, prostatic hypertrophy, glaucoma and hyperthyroidism. Drug-drug precautions: monoamine oxidase inhibitors, other sympathomimetic drugs.
Guaiphenesin	Improvement with respect to cough frequency and severity.	Drug-disease precautions: hepatic impairment, renal impairment, gastrointestinal ulceration.

  - The applicant stated that amongst the three active ingredients, accidental overdose was most common with paracetamol, and that the risk of overdose could be reduced by a smaller pack size. The evaluator noted that this claim appeared to be appropriate.
  - The minimisation of risks of ingestion of PPGC powder by children of 12 years or less, was not discussed in the application.

- XXXXX:
- Noted that the applicant acknowledged additional risks associated with phenylephrine use in patients with cardiovascular disorders or depression. As a sympathomimetic, phenylephrine may cause increases in blood pressure and / or heart palpitations. XXXXX.

- Noted the assertion that guaiphenesin, when used at its recommended doses, posed little or no risk. The applicant contended that although hepatic impairment, renal impairment and gastrointestinal ulceration were listed as risks; the incidences of these adverse events (AEs) were low. Excessive guaiphenesin consumption at high doses was associated with the development of kidney stones and from animal studies, guaiphenesin appeared to have porphyrinogenic effects, however no cases were documented to date.

UK Medicines and Healthcare products Regulatory Agency (MHRA)

- From July 1963 to March 2009, AEs associated with paracetamol, phenylephrine and guaiphenesin were paracetamol (7942), phenylephrine (437) and guaiphenesin (436). Fatal cases included 3 per cent for paracetamol, 3 per cent for phenylephrine (due to cardiac disorders, renal and urinary disorders and respiratory disorders) and 0.4 per cent for guaiphenesin (due to blood disorders and muscle and tissue disorders) and were associated with single active and multiple active formulations, respectively.
- A specific PPGC formulation was implicated in XXXXX AE report, which consisted of complaints of blotchy rash, chest tightness, facial swelling, hypotension, itchy rash and peak flow decreased. The case was considered medically significant due to hypotension and decreased peak flow. The patient recovered without any sequelae. XXXXX.

Australia and NZ consumer reports from the applicant

- The application stated that XXXXX callers reported AEs. There were 3 reports for PPGC powder preparations. The AEs were cough, inefficacy and vomiting. There were no reports of AE to other PPGC preparations or to paracetamol+phenylephrine combination with decongestant products.

Periodic Safety Update Report (PSUR)

- PSUR XXXXX AE in a total of XXXXX patients. XXXXX events in XXXXX cases were considered to be serious. The report concluded that there were no safety concerns with the products. There were no changes to contra-indications, precautions, warnings or adverse drug reactions for cold and flu + chesty cough PPGCs during the period of the PSUR report.

ADRAC

- The applicant asserted that there were no reports of AEs to PPGC.
- There were 2 case reports from 1973 to August 2008, attributed to guaiphenesin as a single active ingredient while there were 81 case reports to guaiphenesin combination products. The AEs to guaiphenesin alone were: urticaria, face oedema, pruritus and oedema peripheral.

- No AEs associated with paracetamol, phenylephrine and guaiphenesin were identified by the NZ Centre for Adverse Reactions Monitoring.
- The applicant concluded that paracetamol+phenylephrine combination and guaiphenesin as a single ingredient was not associated with high incidences of AEs. It further contended that the incidence of AEs for the PPGC was not expected to be higher. Based on the evidence presented, the evaluator agreed that this claim appeared to be appropriate.

(c) Potential Hazard

- The applicant claimed that since paracetamol, guaiphenesin and phenylephrine hydrochloride singularly were not known to cause sedation, the PPGC was also not expected to pose a hazard with respect to sedation. The evaluator noted that this claim appeared to be appropriate.

(d) Extent and Pattern of Use

- Noted that paracetamol, phenylephrine and guaiphenesin have been extensively used in OTC cold and flu preparations. The majority of phenylephrine and guaiphenesin products contained various combinations of phenylephrine with antihistamines, cough suppressants, and / or vitamins.
- Also noted that PPGC powder preparations were first registered in Australia in February 2007. It was classified for general sale in NZ since January 2007. In the UK, the product was available through grocery stores.

(e) Dosage and Formulation

- Noted that PPGC powder contains paracetamol XXXXX, phenylephrine hydrochloride XXXXX and guaiphenesin XXXXX.
- PPGC capsule preparations contain paracetamol XXXXX, phenylephrine hydrochloride XXXXX and guaiphenesin XXXXX.

(f) Need for Access

- The applicant asserted that a third of Australians live in rural areas, and less than a third of pharmacists practice there, therefore there was need for greater accessibility to options of medications available for self-medication.
- As cold symptoms were generally of short duration (4 to 9 days) and resolved spontaneously without sequelae, they were easy to self diagnose and self-medicate.
- Currently small packs of single active analgesic / antipyretics with or without phenylephrine were exempted from scheduling, but they did not contain an expectorant. Therefore consumers would have to buy at least two products to treat symptoms of colds that were associated with a chesty cough. Guaiphenesin liquid formulations were also available for open sale as a single ingredient.

(g) Potential for misuse / abuse

- Noted that phenylephrine differs structurally to phenylpropanolamine. It is not easily converted to methamphetamine and as such it did not have the potential for abuse. It is more structurally similar to adrenaline than amphetamine.
- At therapeutic doses phenylephrine is a selective alpha-l agonist and does not cause significant central nervous system stimulation.
- The other 2 actives, paracetamol and guaiphenesin were not known to be substances of abuse.
- The evaluator reiterated the potential issue of the sachet formulation to being used outside of the labelled indications for dosing in children.

(h) Purpose for which the Substance is to be used

- Relief of cold, flu and chesty cough symptoms, such as blocked nose, headache, fever, chesty cough and sore throat.

Applicant's Response

The applicant provided a comment to the evaluator's concern about a possible risk that the sachet formulation may be inadvertently administered in children of 12 years and under, was unfounded. The applicant asserted that:

- Currently, sachets containing either paracetamol only or the paracetamol+phenylephrine combination, when not labelled for the treatment of children under 12 years of age were already exempted from scheduling, the latter since 2007.
- Addition of guaiphenesin which was already exempted was not expected to add further risk.
- PPGC products were already available as general sales product in the UK since 2002 and NZ since 2005. Pharmacovigilance data from these countries did not reveal any potential problem in regard to inadvertent use in children under 12 years to date.

Pre-meeting Submissions

XXXXX all opposed the proposed exemption for PPGC.

XXXXX reasons for opposing the exemption are summarised below:

- Asserted that no credible efficacy data and only limited safety data were published on the use of PPGC in the general population.
- Noted that the TGA had recently issued a consultation document reviewing the efficacy and safety of cough and cold medicines ('Labelling and packaging of cough and cold medicines – proposed changes to requirements', 22 October 2009). The report commented that there were no studies of guaiphenesin in children that

demonstrated its effectiveness, and of four studies in adults, mainly with chronic respiratory conditions, the evidence was equivocal.

- Asserted that if a decision was made to exempt PPGC from scheduling, it would contradict the current TGA stance of increasing restrictions for over-the-counter (OTC) cough and cold medicines due to safety and efficacy concerns.
- Stated that increasing access by the general public to combination products in supermarkets put the Australian public at risk, as there was no access to pharmacist advice. Such unrestricted access might lead to an increase in AE with PPGC products, and potential off-label use by patients (for example in children, as these was reduced access to children's cold and flu products with the advent of many 'under 2 years' medicines becoming Schedule 3 products).

XXXXX argued that the addition of a third active ingredient increased the likelihood of therapeutic duplication by consumers who may take multiple products for the treatment of cold and flu symptoms. Maintaining the status quo, whereby PPGC was available from pharmacies, would minimise the risk of inadvertent therapeutic duplication.

XXXXX also noted that cough in conjunction with nasal congestion and pain / fever may indicate a more severe underlying pathology than nasal congestion and pain / fever alone. A patient suffering from a productive cough should seek the advice of a health professional that assessed their symptoms and recommended the most appropriate treatment (including referral to a medical practitioner if necessary).

XXXXX also stated that products in sachet formulation (particular those containing multiple active ingredients) must not be available from an unscheduled environment as there may be greater potential for consumers to not regard them as therapeutic goods (particular where products present as 'hot lemon drinks').

XXXXX asserted that the ready access to paracetamol products without the opportunity for health professional intervention was of considerable concern and was a health issue for Australia. In addition, particular reference was made to 52E, including:

(b) Risks and Benefits

- Concerned at having an additional exempted paracetamol preparation available for more indications. Asserted that the risk of accidental paracetamol overdose may lead to liver damage because people were unaware that they may be duplicating paracetamol doses by taking products for different indications.
- Paracetamol was one of the most frequently used drugs in Australia and was used in many forms either alone or in combination with other drugs. It was available in many OTC analgesic and cough and cold products, which were also available from supermarkets in pack sizes of up to 24 units.
- Paracetamol was the most common means of drug overdose in the UK. Was concerned for those people who inadvertently overdose because they take several

different medicines containing paracetamol without being aware of the paracetamol content.

- The USFDA had been concerned about the public health problem of liver injury related to the use of OTC and prescription paracetamol and coordinated a meeting of an advisory committee in June 2009 to consider the matter. This meeting advised that nearly half of the paracetamol overdose cases in the USA were due to accidental overdose and identified the following as contributing factors:
  - Consumers attempting to treat different conditions or symptoms with multiple choices among products containing paracetamol, not realising that paracetamol was an ingredient common to each product.
  - The association between paracetamol and liver injury was not common knowledge.
  - Extensive retail availability may contribute to the perception that the ingredient was unlikely to be harmful.

- Noted that the USFDA solution to this issue has been to mandate that active ingredients are prominently displayed on packs and that they must also include a warning of severe liver damage. XXXXX argued that although this may have some impact, it did not believe this would resolve the problem as many people either did not read or understand the information contained on a pack. Poor health literacy had been identified as a major factor in adverse outcomes from medicine misuse.

(e) Dosage and Formulation

- Noted that paracetamol products traditionally came in units of 500 mg and labels used to include a warning 'not to exceed eight units of paracetamol per day'. Current available products could have significantly more paracetamol than 500 mg per unit and the old warning was no longer appropriate or accurate.
- This variation in paracetamol content per unit may confuse consumers and they may be unaware that they were taking too much paracetamol. It was also becoming more difficult for health professionals to warn users in an easy to understand way.

(f) Need for Access

- Maintained its assertion that people with coughs and colds already had extensive access to treatments through the community pharmacy network and that the benefits with increasing access did not outweigh the risks.

(g) Purposes for which a Substance was to be used

- It believed that symptoms which included a chesty cough were best managed in an environment that facilitates the intervention of a health professional.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (b) risks and benefits, (e) dosage and formulation and (f) need for access.

The Committee first discussed the potential risks from PPGC. A Member noted that PPGC preparations were available in the UK and NZ as general sales products and there were no reports of significant AEs associated with these products. Another Members commented, however, that although only a small number of AEs were reported in relation to PPGC in the UK, there was a high number of AEs reported for paracetamol, phenylephrine and guaiphenesin as single actives and therefore questioned the impact of all active compounds combined together on the number of AEs, if available unscheduled. Another Member noted a related concern had been raised in the pre-meeting submissions – that increased access to PPGC by the general public without a pharmacist's advice being available, might result in an increase in cases of AEs. In response, several Members reiterated the evaluator's comment that no safety concerns for the paracetamol+phenylephrine combination or guaiphenesin as a single active had been reported through TGA.

Members then discussed two additional specific concerns relating to PPGC:

- A Member had some concerns about the risks of long term use of PPGC sachet powder preparations containing high doses of paracetamol. Other Members noted, however, that this dosage was already available in existing exempted paracetamol sachet preparations, which the Committee had previously been satisfied meet the requirements for being unscheduled.
- Several Members also noted the evaluator's concerns as to whether there may be an increased risk to children under 12 from such an unscheduled formulation (i.e. a 'hot lemon drink'). A Member was also concerned about the potential risk of off-label use of PPGC sachets, particularly in children, as so many cold and flu medicines for children under 2 years of age were now Schedule 3 products. It was recalled, however, that the applicant had advised that the label would include restrictions against use by children 12 years of age or less. Members generally agreed, therefore, that any restriction against use by children was best addressed by the regulator.

Members then discussed the more general concern of consumers self treating their different cold or flu symptoms with multiple products, unaware that these products all had an active ingredient in common (paracetamol) and therefore risking liver injury related to inadvertent overdose. A Member noted that his had been a recent concern for the USFDA. In light of these concerns, the Member suggested that perhaps only single active ingredient products should be available unscheduled for the treatment of cough, cold and flu and the availability of combination products should be restricted to at least Schedule 2. The Member argued that products with single active ingredients were less ambiguous to the general public and, with PPGC in particular, having a third active ingredient added yet another layer of complexity in terms of risks of inadvertent

therapeutic duplication by patients who might be taking several paracetamol-based products. Members note, however, that the matter before the Committee at his time was the scheduling of PPGC, not market approval for a particular product presentation, and that this concern over multiple paracetamol products being available unscheduled was best left to the regulator to address when considering labelling packaging (noting that the USFDA strategy to deal with this concern had primarily bee through labelling).

A Member also queried whether there may be a concern with the safety profile of phenylephrine, particularly in subjects with CV problems or on an anti-depressant treatment, and if there may be potential for abuse. Another Member asserted, however, that phenylephrine was not expected to cause sedation, and therefore, had limited potential for abuse – noting that the Committee had been previously satisfied of the low risk of this active when it exempted certain paracetamol+phenylephrine combinations from scheduling (and that the regulator currently had certain mandated labelling in place for phenylephrine products which sufficiently mitigated the other concerns).

The Committee generally concluded, therefore, that the risk from PPGC was unlikely to be significantly different to that of the currently unscheduled paracetamol+phenylephrine preparations. It was noted that paracetamol was the most toxic single active ingredient in PPGC products and the addition of guaiphenesin was unlikely to exacerbate this toxicity.

Members then examined the potential benefits of allowing PPGC to be unscheduled, with an initial discussion about the efficacy of PPGC. A Member suggested that perhaps the Committee should be cautious, noting that the TGA was currently reviewing the evidence of efficacy for a number of OTC preparations for the short-term symptomatic relief of colds, chills and influenza including chesty coughs. Other Members noted that this was an ongoing review by the TGA and had yet to be finalised. The Committee generally agreed that, at this time, it had before it at least some evidence suggesting efficacy for PPGC, and that any further questions on efficacy for a particular product would be a matter for the regulator to consider.

Several Members also noted that it was correct that current paracetamol combination products available in the market did not provide chesty cough and cold relief in a single product and that this necessitated a patient to take two products to have relief of these symptoms. There was general agreement that there was likely to be at least some small benefit from allowing unscheduled access to PPGC.

The Committee generally agreed that there was sufficient data at this time to justify extending the current scheduling exemption for paracetamol+phenylephrine combinations to also included guaiphenesin, noting the low risks and at least some small benefits from allowing unscheduled access to certain PPGC preparations.

RESOLUTION 2010/58 - 21

The Committee decided to extend the current exemption for certain paracetamol+phenylephrine combination products to also include combinations containing guaiphenesin.

Schedule 2 – Amendment

PARACETAMOL – Amend entry to read:

PARACETAMOL for therapeutic use **except**:

(a) when included in Schedule 4;

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

(i) enclosed in a primary pack that contains not more than 12 such powders or sachets of granules;

(ii) compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

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

(iv) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and / or guaiphenesin; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and / or guaiphenesin or when combined with effervescent agents) when:

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

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

(iii) compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

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

(v) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and / or guaiphenesin.

12.2 SUSDP, PART 5

12.2.1 ADRENALINE

PURPOSE

The Committee considered an Appendix H entry for adrenaline auto-injector preparations.

BACKGROUND

Adrenaline is a direct acting sympathomimetic with effects on both alpha and beta adrenergic receptors. Major effects include increased systolic blood pressure, reduced diastolic pressure (thus resulting in increased pulse pressure), tachycardia, hyperglycaemia and hypokalaemia. Adrenaline is a powerful cardiac stimulant and has both antihistaminic and bronchodilatory actions.

Adrenaline is used in the emergency treatment of anaphylaxis (acute severe allergic reaction), an immediate-type hypersensitivity reaction affecting multiple organ systems and characterised by life threatening upper airway obstruction, bronchospasm and/or hypotension. Anaphylaxis has a rapid onset and requires urgent treatment, most frequently outside of a medical setting.

At the January 1955 meeting, the Committee listed adrenaline in Schedules 2 and 3 for preparations of less than 1 per cent and in Schedule 4 for preparations containing more than 1 per cent. At the May 1956 meeting, the Schedule 2 entry was deleted and the Schedule 3 entry refined to exempt concentrations of less than 0.01 per cent.

In August 1985, the Committee decided to amend the Schedule 3 and 4 entries for adrenaline to raise the exemption to preparations containing 0.02 per cent, stating that such a low level is not toxic and does not pose a health risk except in diabetics.

At the February 1999 meeting, the Committee recommended that New Zealand harmonise with the Australian adrenaline scheduling. New Zealand subsequently agreed to this recommendation.

DISCUSSION - SUBMISSIONS

XXXXX submitted an application requesting an Appendix H listing for adrenaline auto-injector preparations containing 0.15 mg or 0.3 mg of adrenaline for use in the emergency treatment of acute severe allergic reactions. The application did not request any changes to the wording of the current schedule entries. The application is summarised below:

- Intramuscular adrenaline is the treatment of choice for the management of an acute anaphylactic reaction. Pre-determined doses of adrenaline can be easily, quickly and accurately delivered by an adrenaline auto-injector.
- Peak professional and consumer advocacy organisations responsible for allergy care in Australia recommend the use of adrenaline auto-injectors for administering adrenaline in the community setting.
- Regular education and training in using an auto-injector is required to ensure that the correct administration technique becomes automatic in times of high stress. As a large proportion of patients at risk of anaphylaxis are children, understanding and familiarity with the operation of the auto-injector is required by a range of care givers and adults.
- Improved understanding in device use would also facilitate a reduction in injury from misuse and accidental injection, promote familiarisation and timely use of the auto-injector, and ultimately allay anxiety in patients and care givers.
- Currently, the Therapeutic Goods Advertising Code restricts direct communication with potential users and care givers. As a result, the coordination of optimal education and training programmes directed to non healthcare professionals can be difficult. Partly as a consequence of this, current education and training programmes are fragmented and inconsistent across organisations and states. Furthermore, with the increasing prevalence of anaphylaxis in Australia, the expected increase in demand for education and training is expected to further stretch resources and initiatives.
- Inclusion of adrenaline in Appendix H will promote training and familiarisation and optimise the safe and effective use of auto-injectors in the community. Training materials are proposed to educate patients and carers about allergy awareness, the recognition of signs and symptoms, appropriate anaphylaxis management and specifically how to use the device.

The applicant also addressed matters under 52E, including:

(a) Toxicity and Safety

- Asserted that as the adrenaline auto-injector is in Schedule 3, significant consideration of its therapeutic use and risks and benefits has already been made by the Committee.

- Adrenaline is relatively safe when used under appropriate circumstances and serious side effects are not usually a concern for otherwise healthy persons. As the adrenaline auto-injector is intended for use in life-threatening emergencies, contraindications are relative.
- The adrenaline auto-injector must not be used intravenously as cerebral haemorrhage may occur due to a sharp rise in blood pressure.
- Common symptomatic adverse events include anxiety, restlessness, tachycardia, respiratory difficulty, tremor, weakness, dizziness, headache, dyspnoea, cold extremities, pallor, sweating, nausea, vomiting, sleeplessness, hallucinations, palpitations, fear and flushing or redness of face and skin. Psychomotor agitation, disorientation, impaired memory and psychosis may occur. Potentially fatal ventricular arrhythmias, including ventricular fibrillation may occur and severe hypertension may lead to cerebral haemorrhage and pulmonary oedema.
- In specific populations, contraindications include anginal pain, ventricular extrasystoles, tachycardia or fibrillation, decompensation, phenothiazine-induced circulatory collapse and prostatic hypertrophy, syncope, ECG changes, rigidity and tremor.
- Administration of adrenaline to pregnant women and women of childbearing age has shown no proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus. Adrenaline is excreted in breast milk and may delay the second stage of labour by inhibiting contractions of the uterus.

Drug interactions

- The effects of adrenaline may be potentiated by tricyclic antidepressants, thyroid hormones, monoamine oxidase inhibitors, propranolol and some antihistamines. Negative drug interactions have been recorded when adrenaline was administered to patients also receiving other sympathomimetic agents, alpha-adrenergic blocking agents, non-selective beta-blocking drugs, digoxin, hypoglycaemic agents, quinidine halothane and other anaesthetics such as cyclopropane and trichlorethylene.
- Adrenaline is physically incompatible with alkalis, metals, oxidising agents, sodium warfarin, hyaluronidase and forms polymers with sodium bicarbonate.

(b) Risks and Benefits

- Public health benefits associated with the listing of adrenaline auto injectors in Appendix H include the minimising of potential risks associated with use of auto injectors, better community education on the use of the device, the promotion of access for early and immediate self administration and increased device familiarity for patients and their carers, which may alleviate anxiety.

(c) Potential Hazards

- The main hazards associated with adrenaline auto-injectors are needlestick injuries and a lack of effect due to incorrect use (including misadministration and no administration). The applicant contends that a large proportion of reported "accidental injection" events could be avoided through more coordinated and readily available education on device use. Further investigation by XXXXX suggests that reports of "lack of effect" are largely due to unfamiliarity with, or lack of training in, the method of administration of the device.
- As different auto-injectors require different methods for administration, clear instructions, education and planning are essential to minimise possible delay in administration and/or incorrect injection.

(d) Extent and Patterns of Use

- Adrenaline auto-injectors were first registered in Australia in 1993 for the emergency treatment of anaphylactic reactions to insect stings through immediate self administration by individuals with a history of hypersensitivity to insect stings. In August 2003, this indication was amended to include the emergency treatment of anaphylaxis due to drugs or other allergens in addition to insect stings. The device is intended for use by non-medically trained individuals of all backgrounds.
- Auto-injectors are listed on the PBS as an authority required listing and the majority of device purchases are subsidised by the PBS.
- Adrenaline auto-injectors are also registered in USA, EU, Japan, Canada and New Zealand. Although the device is a prescription only medication in the US this does not preclude direct to public advertising.

(e) Dosage and Formulation

- Adrenaline auto-injectors are available in adult and child dosages containing one auto-injector per pack.
- For adults, each auto-injector contains 2 mL adrenaline injection 1:1,000 USP and is designed to deliver a single 0.3 mL dose of 300 micrograms.
- For children, each auto-injector contains 2 mL adrenaline injection 1:2,000 USP and is designed to deliver a single 0.3 mL dose of 150 micrograms.

(f) Need for Access

- Auto-injectors are the primary means of adrenaline administration in the community and for those at risk of anaphylaxis there is no treatment alternative, unless ampoules and syringes are provided to patients.
- Effective management of information and consumer support is needed for individuals involved with the daily care of a patient at risk of anaphylaxis (including family, extended family, school staff, child care staff, camp, restaurant and pharmacy staff) as

these groups are often required to administer the auto-injector when an event occurs. Largely, problems arise because individuals may not be calm enough to read the labelling on the device in an emergency situation, instead relying on intuition and familiarity which can only be instilled with frequent training and education.

- Advertising will assist in relevant groups receiving specific education, training and information. Direct communication will also increase the resources available for training, resulting in reduced confusion and improved compliance with device use. The applicant has already received conditional support from XXXXX to develop training materials.

(g) Potential for Misuse

- The submission asserted that adrenaline auto-injectors have already been considered by the Committee to be a substantially safe medication with a low abuse potential, low potential for harm from inappropriate use and a low incidence of severe adverse effects, but one which requires professional advice and counselling.
- The likelihood of the wider promotion of adrenaline auto-injectors leading to inappropriate patterns of use is low given the nature of the medicine and device, and its very low inherent risk of abuse or addiction.

(h) Purpose

- Adrenaline auto-injectors are used in the emergency treatment of anaphylaxis.

(i) Additional matters

- There is a need for further education and training for pharmacy staff, ensuring pharmacy assistants are better informed of anaphylaxis and auto-injector-specific resources available within the pharmacy, thus helping to close the knowledge gap. The applicant states that such education and training needs to also extend to other carers including school staff.

Evaluation Report

The evaluator advised that, as the suitability of adrenaline auto-injectors for inclusion in Schedule 3 had already been determined by the Committee, the evaluation focussed only on issues relevant to the Appendix H listing proposal.

The evaluator supported the proposal to include adrenaline auto-injectors into Appendix H based on the following:

- it is appropriately argued that the efficacy and safety of adrenaline auto-injectors depends on an appropriate and timely response to an acute anaphylactic episode and its effective use comes with the need for commitment to education and re-familiarisation for both patients and their carers, especially as the device is administered in times of high anxiety;

- the coordination of optimal education and training programmes directed to non healthcare professionals is restricted and current available education and training programmes are fragmented;
- advertising will improve education regarding other aspects of auto-injectors, such as carrying the device at all times and regular checking of expiry date;
- there is a public health benefit in improving knowledge of allergy in the broader community as recurrent anaphylactic episodes may occur away from home without a parent present;
- needlestick injury and lack of effect risks may be improved with more coordinated and readily available education; and
- that given the nature of the medicine and device, and its very low inherent risk of abuse or addiction, there is low potential that wider promotion of adrenaline auto-injectors will lead to inappropriate patterns of use.

Pre-meeting Submissions

XXXXX opposed the inclusion of adrenaline auto-injectors in Appendix H, stating that:

- the current Schedule 3 entry exists so that in emergency situations adrenaline may be supplied without any delays that would arise if it was only included in Schedule 4;
- although it is entirely appropriate that adrenaline auto-injectors can be purchased from a pharmacy without a prescription, the initial diagnosis and ongoing management of patients who suffer severe acute allergic reactions (including anaphylaxis) should be handled, as a minimum, by a general practitioner; and
- direct to consumer advertising has the potential for inappropriate requests to be presented to pharmacists which may deter some patients from having the necessary initial and ongoing assessments of their allergic conditions.

XXXXX supported the applicant's submission with the proposed limitations. However, XXXXX was keen to ensure any messages to consumers would be conveyed in a manner that highlighted the exact purpose of use of adrenaline auto-injectors and that they do not inadvertently send confused or unintended messages to those who do not have a possible future therapeutic need.

XXXXX expressed XXXXX concerns with the inclusion of adrenaline auto-injectors in Appendix H. Although XXXXX acknowledged some merit in raising public awareness of the availability of adrenaline auto-injectors for the treatment of acute severe allergic reactions, a number of concerns were raised, including:

- adrenaline auto-injectors are listed on the PBS and need for its use has been initially assessed by, or in consultation with, a clinical immunologist, allergist, paediatrician or respiratory physician;

- there is a potential conflict of interest with the PBS if an item listed on the PBS is able to be advertised direct to consumers. It was recommended that this conflict be clarified before any decision was made – the Committee subsequently confirmed that there are other Schedule 3 substances in Appendix H which are also listed as PBS items;
- consumers have a poor understanding of allergies and there is a risk that direct to consumer advertising may prompt people with non-anaphylactic allergies to seek an adrenaline auto-injector. When questioned on medicine allergies, it is not uncommon for a consumer to advise that they have a drug allergy when in fact it is a drug sensitivity or an adverse drug reaction;
- strategic advertising could promote adrenaline auto-injectors in such a way that pharmacists will need to spend significant time and effort in assessing the appropriateness of the request; and
- whilst easy to use, training / counselling is necessary for effective use of adrenaline auto-injectors, and information and training for the XXXXX brand is available online.

XXXXX also reiterated XXXXX advocacy for a Schedule 3 'Notifiable' category.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits, (d) extent and pattern of use, and (f) need for access.

The Committee agreed that the education of patients and carers in the effective use of auto-injectors was important. However, less clear was the need to allow brand name advertising through an Appendix H listing to achieve this education. A Member asserted that education is usually provided by the doctor when the auto-injector is first prescribed and further information is also available from the dispensing pharmacist. Other Members asserted that while the public is not generally well educated on issues relating to acute anaphylactic reactions nor trained to administer adrenaline, those affected are usually highly educated regarding the issues (particularly parents).

The Committee also noted that there were already a number of avenues for adrenaline auto-injector training. While there are restrictions regarding branded advertising, Members noted that education groups are allowed to provide information on adrenaline auto-injectors, independent of brand. A Member particularly noted the recent roll-out of a substantial Western Australian education program on this issue. Another Member noted that a number of effective programs were supported by various jurisdictions and asserted that the applicant's argument regarding the need for Appendix H listing to address an unmet education need was overstated. The Committee generally agreed, therefore, that there was less potential benefit from Appendix H listing than was argued in the application.

Several Members also supported the concern raised in some pre-meeting comments that advertising of auto-injectors may target or pressure the general community into purchasing auto-injectors without need and cause an influx of inappropriate requests to pharmacists. Another Member also asserted that, with the availability of new types of auto-injectors, advertising has the potential to cause confusion for patients regarding the different methods of administration.

A Member also asserted that it should be kept in mind that auto-injectors were included in Schedule 3 to facilitate emergency access for a specific group of people rather than the usual purpose of the majority of Schedule 3 listings i.e. to provide the community with access to a beneficial therapeutic option which requires professional advice but not a prescription. The Member was concerned that advertising could undermine this distinction.

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The Committee decided that the inclusion of adrenaline in Appendix H is inappropriate.

12.2.2 PANTOPRAZOLE

PURPOSE

The Committee considered a proposal to include pantoprazole in Appendix H.

BACKGROUND

Pantoprazole is a proton pump inhibitor (PPI) with actions and uses similar to those of lansoprazole (agenda item 16.1.6) and omeprazole (agenda item 16.1.7). It suppresses secretion of gastric acid by inhibiting the enzyme system of hydrogen / potassium adenosine triphosphatase (H+/K+ ATPase), the ‘proton pump' of the gastric parietal cell. It is indicated for the treatment of peptic ulcer disease and gastro-oesophageal reflux disorder (GORD).

Pantoprazole was first scheduled in Schedule 4 in February 1995.

At the June 2005 meeting, the Committee agreed to include pantoprazole in Schedule 3, 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. A delayed implementation date of 1 May 2006 was set down (this was subsequently further delay to 1 May 2008). An Appendix H listing was not supported as the Committee felt there was insufficient information at the time to allow direct-to-consumer advertising. The Committee agreed that it would not consider an Appendix H listing until patterns of use of pantoprazole as a Schedule 3 medicine had been established.

At the February 2009 meeting the Committee again rejected a proposal to include pantoprazole in Appendix H. The Committee noted there were insufficient data from

Australian marketing to allow conclusions to be drawn on risks and benefits, potential hazards, extent and pattern of use and other relevant matters, in the context of advertising and public health benefit. As such, no conclusions on the likelihood of improvements in health outcomes could be drawn for pantoprazole at that time.

The Committee recommended rabeprazole to be included in Schedule 3 at the June 2009 meeting. However, a requested Appendix H listing was rejected for the same reasons as for pantoprazole in February 2009.

DISCUSSIONS - SUBMISSIONS

Applicant's Submission

XXXXX requested the inclusion of pantoprazole in Appendix H. Members particularly noted the following arguments from the application:

- Pantoprazole was approved in 73 countries worldwide, and extensive data were available to support its favourable safety profile. OTC availability of pantoprazole for short-term treatment of reflux symptoms has been available in Europe since June 2009 and this included direct-to-consumer advertising.
- The scientific background, product background, registration history were adequately described in the prior application (February 2009 meeting) for Appendix H listing. In addition, the applicant asserted that the safety data on OTC use and self-management had been recognised by the rescheduling decision made by the Committee.
- The application also discussed the currently available evidence regarding pharmacokinetic interactions between pantoprazole and clopidogrel, asserting that this had been shown to be less likely to occur with pantoprazole than others PPIs.
- Heartburn and acid reflux was a very common condition. The majority of sufferers self-medicate despite the fact that up to 50 per cent will experience symptoms at least weekly.
- Consumers currently self-treat with medicines available in supermarkets or OTC. Antacids were intended for occasional use; as their effect was short-lasting, they were subject to overuse when symptoms were not sufficiently controlled. PPIs were more effective acid suppressors than histamine 2-receptor antagonists (H2RAs) as the acid suppressing ability of H2RAs decreases over time (tolerance development).
- One out of 25 people who were purchasing their heartburn medication in a supermarket should ideally be speaking to their GP. Advertising may well help to drive these patients into the pharmacy where their symptoms would be assessed, resulting in more appropriate medication choice.
- It was likely that advertising of pantoprazole would not substantially change the manner in which patients would be assessed in the pharmacy setting. Pharmacists now have 12 months in-market experience using educational tools and protocols

relating to pantoprazole for heartburn relief. Concerns regarding consumers demanding a therapy that may not be clinically suitable could be mitigated by the pharmacists' advice.

- The current application included data from an audit amongst pharmacists that had demonstrated that pharmacists were using these protocols and that pantoprazole was not provided to every customer. The data indicated that XXXXX per cent of interactions resulted in GP referral for various reasons, and although XXXXX per cent of consumers thought the product would be suitable for them after reading the pack label, only XXXXX per cent actually bought the product after receiving advice from the pharmacist.
- XXXXX showed that a majority of pharmacists agreed that direct advertisement of this product would assist both their customers and their business.
- Acknowledged that the primary purpose of direct-to-consumer advertising of Schedule 3 medicines is the protection of public health and improvement in health outcomes.

The applicant also addressed a number of matters under section 52E, including:

(a) Toxicity and Safety

- This issue was previously addressed by the Committee, in 2005, when it was determined that certain pantoprazole preparations were suitable for listing in Schedule 3.
- Thirteen years of post-marketing surveillance was supplied in the previous Appendix H application. These data demonstrated that pantoprazole tablets were highly unlikely to present a direct danger when used correctly without medical supervision.
- The Adverse Drug Reactions Advisory Committee (ADRAC) advised that the adverse events (AEs) related with the use of pantoprazole between May 2000 to September 2008, and October 2009 to date, recorded a total of 320 cases and none resulted in death (at any dose of pantoprazole). Five per cent of AEs were related to pantoprazole 20 mg, with once case considered to be life threatening, involving dyspnoea. The patient fully recovered after ceasing to take pantoprazole. Another patient suffered anaphylaxis after taking pantoprazole 20 mg.

(b) Risks and Benefits

Safety in OTC use

- Pantoprazole had a low general toxicity and no relevant genotoxicity, carcinogenicity nor reproductive toxicity. Post-marketing surveillance confirmed the safety profile, which included 14 years of prescription use worldwide and 8 years of OTC use in Sweden. The majority of reported AEs had been minor and transient, and mostly referred to gastrointestinal and nervous system disorders such as diarrhoea, nausea, and headache.

- Pantoprazole 20 mg tablets did not present any significant direct danger when used correctly without medical supervision.

Efficacy

- The efficacy of pantoprazole 20 mg had previously been addressed by the Committee, in February 2005. Clinical efficacy had been demonstrated for the treatment of heartburn and acid regurgitation during a XXXXX.

(c) Potential Hazards

- It had already been recognised by the Committee that there was a low hazard potential with the use of pantoprazole 20 mg.
- In the last 12 months, concerns have been raised about an interaction between PPIs and clopidogrel. Members noted that this issue had been previously discussed (see the June 2009 minutes for rabeprazole). It had been reported that omeprazole appeared to have the highest potential for overall drug-drug interactions among PPIs, and rabeprazole and pantoprazole appeared to have the least interaction risk (Khalique, SC & Cheng-Lai, A 2009, 'Drug interaction between clopidogrel and proton pump inhibitors', *Cardiol. Rev.*, vol 17, pp. 198-200).
- It had been found that pantoprazole had no significant effect on clopidogrel. The applicant acknowledges that differing and conflicting results have been published on this topic and that both the EMEA and USFDA had issued statements acknowledging that the situation was currently inconclusive.

(d) Extent and Patterns of use

- The applicant noted the concerns as to whether consumers would use OTC PPIs as directed. Asserted that US marketing data of OTC PPIs supported that consumers accurately self-selected a PPI, complied with the dose regimen and appropriately sought medical practitioner involvement.
- In Australia, pantoprazole 20 mg Schedule 3 has been available for 11.5 months (at the time of application). XXXXX.
- A prior concern raised by the Committee was that overseas OTC use of PPIs did not take into account prescribing patterns in these countries. This was felt relevant because Australia has a relatively high prescribing rate for PPIs on a per capita basis. From the available data, the current OTC sales of pantoprazole 20 mg were only XXXXX of the current prescription use of the same product.

(e) Dosage and Formulation

- Oral, yellow, oval shaped tablets in blister packs of 7 and 14 dosage units.
- XXXXX.

(f) Need for Access

- Pantoprazole 20 mg was expected to provide a significant contribution to patient care by allowing treatment of reflux symptoms like heartburn and acid regurgitation with a product with established safety and improved efficacy as compared to the available OTC antacids and H2RAs.
- The need for access to pantoprazole when supplied as a Schedule 3 had not changed substantially since previously addressed to the Committee.

(g) Potential for Misuse / Abuse

- There was a low potential for abuse from inappropriate use of pantoprazole 20 mg.
- As shown in the previous application, there were only XXXXX of misuse of pantoprazole tablets. XXXXX were serious, XXXXX of which were unrelated to pantoprazole. XXXXX.
- There was no evidence of any abuse or direct addictive effects of pantoprazole. Whereas omeprazole might be used at high doses to prolong the action of central stimulants by inhibiting their metabolism, no such report has been received for pantoprazole.
- A total of XXXXX overdose cases have been reported, none of which resulted in death or permanent disability. There have been no reports of overdose of pantoprazole in Australia since it has been available as a Schedule 3 medicine.

(h) Purpose

- Symptomatic relief of heartburn, acid regurgitation and other symptoms associated with GORD. The applicant reiterated that it did not seek to alter this indication.

In addition, the applicant addressed additional matters, and Members noted the following points:

Potential public health benefits

- An Appendix H listing would enable more specific communication to consumers on how a pharmacist was able to provide them with information about how to appropriately manage their heartburn.
- This would ensure that frequent heartburn sufferers were given access to the most appropriate treatment rather than continuing to endure symptoms without accessing effective therapies (as was thought to be the current practice for many).
- A listing in Appendix H would increase consumer awareness of new medicines, and can directly address any consumer misconception that heartburn did not need medical intervention. The ability to advertise to consumers raised awareness of the fact that the pharmacist was able to provide advice about heartburn management and a more effective treatment option (compared to other currently available products).

Impact of advertising

- Addition of pantoprazole to Appendix H would not result in the advertising for an indication other than those included in the Australian Register of Therapeutic Goods (ARTG).
- Pharmacist intervention was required to assess customer suitability prior to the supply of pantoprazole. Given that, a change in advertising status would not result in a change of the purpose for which the product was to be used.

Responsibilities of pharmacists

- An education program had been developed with representatives from pharmacy, general practice and specialist care (gastroenterology) and rolled out nationwide.
- The pharmacy audit activity has demonstrated that pharmacists were using this set of protocols and algorithms, and that pantoprazole 20 mg was not provided to every customer who claimed to have frequent and/or moderate to severe heartburn symptoms. These tools effectively aid in communication and assist in managing consumer demand and expectation.
- XXXXX agreed that if the product was advertised directly to consumers it would assist both their customers and their business.
- The potential to drive consumers into pharmacy to receive counselling needed to be balanced against the potential to stimulate demand for a product which may not be clinically justified. The applicant asserted that this issue was far less likely to be a concern for pantoprazole, as a comprehensive set of protocols and algorithms have been developed. By using these protocols, pharmacists were not providing pantoprazole to every customer who believed they had frequent and / or moderate to severe heartburn symptoms.

Availability of Consumer Medicine Information (CMI)

- A CMI and package leaflet had already been approved by the TGA.
- If a consumer was judged suitable for pantoprazole, the pharmacist would also provide a verbal summary on how to use the product which would further reinforce the CMI and the package leaflet.

Desire of Consumer to Self-Manage

- Without advertising, consumers may continue to be unaware of the availability of a new, potentially more effective product to manage their condition. The applicant reiterated that advertising would not negatively impact the appropriate use of this medicine because all consumers making a direct product-based request would be subject to questioning by the pharmacist. Adverse consequences of continued self-management amongst those who should ideally be seeing their GP would be negated and overall health outcomes would be improved.

Evaluation Report

The evaluation supported the proposed inclusion of pantoprazole in Appendix H. Points noted by the evaluator in making this recommendation included:

- The Committee had previously accepted that pantoprazole, when used in accordance with the current Schedule 3 indication limitation, was suitable for self-treatment with pharmacist advice.
- A product meeting the requirements of Schedule 3 marketing was launched in late 2008. At that time, a package of educational materials was made available to pharmacists. The educational material had been reviewed and was of generally high standard. Data from an audit of interactions between customers and pharmacists suggested that pharmacists were willing to provide considered advice to potential purchases of pantoprazole.
- Usage data suggested that there was probably relative under-usage of the product in comparison with less efficacious products available in supermarkets, where there was no access to professional advice.
- The present application had provided a reasonable argument in favour of its contention that there were potential public health benefits to be gained by allowing direct-to-consumer advertising. These included the earlier identification of consumers who required medical attention for their GORD, and the more effective treatment of symptoms of those who are suitable for self-medication and who have failed to benefit from antacids and H2RAs.

The Committee also noted the following addition points raised by the evaluator:

- The inclusion in Appendix H needed the demonstration of likely public health benefits from advertising pantoprazole.
- The applicant argued that PPIs were more effective acid suppressors than either antacids (intended for use only for short periods) or H2RAs, and this was accepted by the evaluator.
- The argument followed that PPIs would be a better treatment option for sufferers of frequent heartburn without other atypical GORD symptoms. The evaluator asserted that advertising would address this issue, thus improving public health.
- The evaluator considered the toxicity and safety data of pantoprazole 20 mg when supplied as a Schedule 3 medicine to be supportive.

The evaluator also considered the applicant's arguments to address the matters raised by Committee at the February 2009 meeting. The Committee's reasons for rejection at that time fell into two major categories: benefit to public health and the pattern of OTC use. Members noted the following from the evaluator's discussion on these points:

Benefit to public health

- The need for access to the product on a non-prescription basis had been successfully argued previously and was accepted.
- The applicant pointed out that the ability to advertise pantoprazole would:
  (1) Directly addressed any consumer misconception that heartburn did not required medical intervention.
  (2) Raise awareness that the pharmacist was able to provide advice about heartburn management and a more effective treatment option.
  (3) Encourage heartburn sufferers to talk to their pharmacist at an earlier stage of their disease.
  (4) Improve public health by promoting a better use of professional expertise.
- The evaluator noted that the applicant had not supplied data to support points (1), (2) or (3), but it was reasonable to assume that effective advertising would have these outcomes.
- In relation to point (4), the evaluator noted that XXXXX had developed a training program and treatment algorithm to the recognition of the "red flag" symptoms that indicated that referral to a GP was warranted. The evaluator agreed with the applicant's argument that while these were already available to any consumer who requested pharmacist advice, the key to the advertising was that it would result in a greater proportion of consumers with heartburn seeking such advice and thus benefiting from the treatment algorithm.
- To further support point (4), the applicant supplied data from a pharmacy audit designed to evaluate OTC management of heartburn within retail pharmacy since the launch of pantoprazole 20 mg. The data were suggesting, rather than conclusive, but did support the contention that, when consumers approached pharmacists for advice about heartburn treatments, the advice was based on the pharmacist's professional expertise.

Pattern of OTC use

- Usage data suggested that relatively few consumers have been accessing OTC pantoprazole in comparison to those accessing GPs. A more useful comparison would have been with the number of consumers purchasing OTC heartburn treatments either in the supermarket or in the pharmacy and having an inadequate response to it. Such data would have indicated the size of the unmet need for more effective heartburn treatments in the absence of advertising.
- The gastrointestinal category of supermarket products was growing by about XXXXX per cent per annum, while products in pharmacy were in decline. The application argued that these data supported the contention that most people were self-treating in an environment that did not provide easy access to professional advice. The evaluator agreed that this was a reasonable conclusion.

Comment on the Evaluation Report

The applicant agreed with the conclusions made in the report, however, it wished to also point out:

- Since the application was lodged, there have now been over 15 months of experience with pantoprazole in Australia, and no changes to usage patterns have been report since its application was lodged.
- Reiterated its argument that the advertisement of pantoprazole would result in public health benefits. It added that the evaluator noted that the data provided supports this argument, and that no negative impact would result from advertising pantoprazole.

Pre-meeting Submission

A number of pharmacist professionals XXXXX supported the inclusion of pantoprazole in Appendix H. All four pharmacists have been involved in a pantoprazole audit and have been exposed to pantoprazole 20 mg in the pharmacy for over 12 months. They noted that they were very familiar with the product and have witnessed its safety profile and effectiveness.

XXXXX also supported the inclusion of pantoprazole in Appendix H and made the following points:

- XXXXX had delivery education, training and resources to pharmacists nationally, and consulted regarding consumer-based research since prior to the substance being approved for inclusion in Schedule 3.
- In the community pharmacy setting, non-pharmacist staff members had an important role in assisting with the supply of therapeutic goods and referring the consumer to a pharmacist when required. Appendix H listing for pantoprazole would appropriately enable further investment in education events and resources for non-pharmacist pharmacy staff.
- Appendix H listing would also allow advertising to consumers. It was noted that advertising to the public already occurs for several Schedule 2 and unscheduled products which were used to treat uncomplicated GORD.

XXXXX supported the proposal to include pantoprazole in Appendix H. Members noted the following:

- XXXXX of a pharmacy education campaign for XXXXX on the optimum treatment of gastro-oesophageal reflux.
- The campaign was XXXXX, covering the pharmacist's role and responsibilities in the assessment of products for heartburn, and has been presented at pharmacist education events.

- The non-prescription availability of PPIs such as pantoprazole did not pose any increased risk to patients, but did provide patients with easier access to more effective therapy.
- Treatment for heartburn with antacids, alginates and H2 blockers such as ranitidine, were advertised and available from both supermarkets and pharmacy outlets. The advertising of pantoprazole should encourage people with heartburn to seek pharmacist advice on appropriate therapy and if necessary referral to a doctor.
- In a pharmacy audit XXXXX per cent of pharmacists interventions resulted in doctor referral.
- The listing of pantoprazole in Appendix H would further drive pharmacists' involvement in managing heartburn an GORD, resulting in positive health outcomes.
- An Appendix H listing for pantoprazole would create an environment where pharmacists would become even more involved in managing this common health condition and this would result in positive health outcomes.

XXXXX, a GP, supported the inclusion of pantoprazole in Appendix H, and noted the following:

- Pantoprazole incidence of side effects was equivalent to placebo. The safety profile was no different from ranitidine which was available in supermarkets and was advertised.
- Reiterated that XXXXX had provided pharmacists with education.

XXXXX, reiterated his February 2009 support for including pantoprazole in Appendix H. Noted that since February 2009 a clinical audit conducted in pharmacy has demonstrated that a pharmacy education program has been adopted and pharmacists were playing an important triage role in the management of oesophageal reflux.

XXXXX national reflux guidelines, supported the inclusion of pantoprazole in Appendix H. (Katelaris PH et al, 2002, 'Gastro-oesophageal reflux disease in adults: guidelines for clinicians', *Journal of Gastroenterology & Hepatology*, vol 17, pp. 825-33) and the following comments were made:

- Asserted that a clinical review discussed the concerns regarding masking disease and delaying medical review and concluded that these were the same for non-prescription PPIs as they were for antacids and H2RA. The treatment algorithm described in the paper was comparable to that advised by a pharmacy education program.
- XXXXX of the 2009 pharmacy audit XXXXX on the management of heartburn. The results of this audit indicated that overall, pharmacists were managing consumers presenting with heartburn consistent with the treatment algorithm developed for non-prescription pantoprazole.
- Compared with the more widely available non-prescription heartburn treatments, pantoprazole provided consumers with an incremental improvement in efficacy

without any apparent compromise in safety. Concluded that, if Appendix H conditions were deemed appropriate for other common pharmaceutical agents, it seemed reasonable to afford pantoprazole the same regulatory listing as these.

XXXXX opposed the inclusion of pantoprazole in Appendix H. As noted in its submission to the February 2009 meeting, the consequent direct-to-consumer advertising would most likely impair rather than enhance the ability of pharmacists to satisfactorily fulfil their professional responsibilities in relation to the supply of pantoprazole as a Schedule 3 medicine.

XXXXX acknowledged some benefits for consumer and public from advertising pantoprazole for heartburn and reflux:

- Increased consumer awareness of an effective treatment and may prompt them to seek health professional advice.
- Additionally, it may prompt patients who regularly purchase antacids or ranitidine from supermarkets to consult their pharmacist for more information.

XXXXX reiterated its general concern with regard to Appendix H listing for Schedule 3 drugs, but in this instance, it had few concerns with listing pantoprazole. It separately reiterated its advocacy for a Schedule 3 'Notifiable' category (acknowledging that a decision on creating such a category was not within the per view of the Committee).

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits and (f) need for access.

XXXXX

A Member expressed concerns with recent reports from Australian Adverse Drug Reactions Bulletin which suggested an association between PPIs and increased incidence of fractures. Members also discussed the current uncertainty regarding potential interactions between PPIs clopidogrel. A Member particularly noted the applicant's claim that there has been evidence that clopidogrel interaction occurred to a less extent with pantoprazole than with other PPIs. Another Member noted that the current consideration was regarding inclusion in Appendix H rather a reconsideration of the Schedule 3 entry, and these issues were not particularly relevant in relation to the question of advertising pantoprazole.

Members generally agreed that a key issue in considering inclusion of a substance in Appendix H was whether a significant overall public health benefit would result from advertising. A Member suggested that, in this regard, the applicant's claim (that advertising would prompt patients, who intended to buy medication for GORD, to seek advice from pharmacists) was likely to be a real benefit. The Member noted that advertising may also highlight the options available OTC to alleviate GORD symptoms.

In particular, some Members recalled the applicant's argument that advertising would encourage patients with GORD who have failed to benefit from antacids and H2RAs to talk to a pharmacist and to shift to a more effective treatment. A Member added that this pharmacist interaction may also help with an earlier identification of consumers who might require medical intervention. Other Members remained less convinced that advertising would be of significant benefit, noting a number of concerns detailed below. One Member contended that the ability to advertise did not assure a positive outcome in terms of treatment and patient compliance, and that it might even cause other serious conditions to be overlooked.

Members also discussed the extent of the Australian market experience with OTC pantoprazole noting that an OTC product had only been in available in the Australian market since 2009. A Member asserted, however, that pantoprazole had been available overseas OTC for a number of years and that marketing data from these market indicated that patients were properly self-managing their symptoms. Another Member remained concerned that the basis for a number of claims of benefit from advertising (in bother the application and some pre-meeting submissions) appeared to be solely based on the overseas OTC experience, noting that the circumstances in those countries might not reflect current Australia use patterns.

Members also considered the concern from one pre-meeting submission that advertising of pantoprazole would potentially impair the ability of pharmacists to adequately carry out their professional responsibilities. A Member supported the concern that the pharmacist could be under pressure in managing a large number of sufferers of heartburn and GORD. Another Member asserted that this concern underestimated the professional abilities of pharmacists and commented that XXXXX was well recognised as a provider of helpful educational material elucidating the pharmacists' role and responsibilities in the assessment of OTC products for patients.

A Member also asserted that, while XXXXX generally prefer to not have Schedule 3 products advertise directly to the public, in this instance it seemed that XXXXX had fewer such concerns. A Member was a little concerned that these positive recommendations were all coming from pharmacists who had participated in a pharmacy audit established in conjunction with XXXXX.

The applicant's claim that advertising directly to consumers would assist a pharmacists' business was considered not relevant by the Committee.

An editorial correction to the Schedule 3 pantoprazole entry in the SUSDP was separately considered under item 21.1.2 Editorial amendments to pantoprazole and rabeprazole. The amendment was to include the wording 'per dosage unit' for clarity and consistency.

RESOLUTION 2010/58 - 23

The Committee decided that the inclusion of pantoprazole in Appendix H was inappropriate.

13. MATTERS REFERRED BY THE REGISTRATION PROCESS FOR PRESCRIPTION MEDICINES

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY NDPSC)

13.1.1 CERTOLIZUMAB PEGOL

PURPOSE

The Committee considered the scheduling of certolizumab pegol.

BACKGROUND

Certolizumab pegol is a pegylated tumour necrosis factor (TNF) inhibitor (specifically TNF-alpha), which results in an interference in the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide.

Certolizumab pegol is indicated for the treatment of adults with moderate to severe active rheumatoid arthritis (RA). It is also used in maintaining clinical response and reducing signs and symptoms of moderate to severe Crohn's disease in adults who had inadequate response to conventional therapy. Certolizumab pegol is also under investigation in the treatment of psoriasis.

DISCUSSION - SUBMISSIONS

At its October 2009 meeting, the Australian drug Evaluation Committee (ADEC) (recently replaced by the Advisory Committee on Prescription Medicines) approved a submission from XXXXX for certolizumab pegol XXXXX injection, solution 200 mg / mL for the treatment of moderate to severe RA in adult patients:

- combined with methotrexate in case of either an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs; or
- as monotherapy in case of a contraindication or intolerance to methotrexate.

ADEC noted that:

- certolizumab pegol is most beneficial when used in combination with methotrexate, except in cases where methotrexate is not tolerated. ADEC recommended maintenance doses of 200 mg subcutaneously every 2 weeks or 400 mg subcutaneously every four weeks, when combined with methotrexate;
- XXXXX.

Adverse reactions

According to the Poisindex monograph for certolizumab pegol, common adverse reactions include upper respiratory infections (for example nasopharyngitis, laryngitis, viral infection), urinary tract infections (including bladder infection, bacteriuria, cystitis), and arthralgia.

Less commonly, certolizumab pegol therapy is associated with angina pectoris, dysrhythmias, cardiac failure, myocardial infarction, myocardial ischemia, pericardial effusion, pericarditis, bleeding and injection site reaction, alopecia totalis, dermatitis, erythema nodosum, urticaria, abdominal pain, diarrhoea, intestinal obstruction, nephrotic syndrome, renal failure, optic neuritis, uveitis, retinal haemorrhage, anaemia, leukopenia, pancytopenia, lymphadenopathy, thrombophilia, elevated liver enzymes, hepatitis, seizure, peripheral neuropathy, and anxiety. Tuberculosis (TB), including disseminated and pulmonary TB (in some cases fatal), has also been reported.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards and (h) purpose for which the substance is to be used.

The Committee agreed that the involvement of a medical practitioner is required for the supply of certolizumab pegol.

RESOLUTION 2010/58 - 24

The Committee decided to include certolizumab pegol in Schedule 4.

Schedule 4 - New entry

CERTOLIZUMAB PEGOL.

13.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

No items.

14. OTHER MATTERS FOR CONSIDERATION

14.1 MERCUROCHROME / MERBROMIN

PURPOSE

The Committee considered a request to clarify the scheduling of mercurochrome.

BACKGROUND

Merbromin (marketed in Australia as mercurochrome solution) is a mercurial antiseptic that has been used for disinfection of skin and wounds. It is currently available in 1, 2 and 10 per cent solutions.

Mercurochrome was first scheduled at the August 1989 meeting when the Committee decided to include it as a new entry in Schedule 6 for the treatment of animals, in preparations for topical use. The meeting minutes do not record any discussion of the reasons for this decision. Nor was there any record of why the trade name was used rather than merbromin.

At the February 1995 meeting, an entry for mercurochrome was added under Appendix E, to improve consistency with the entry for mercury organic compounds in preparations for human external use.

At the November 1998 meeting, the Committee recommended that New Zealand delete its entry for mercurochrome and essentially harmonise with Australian scheduling for human therapeutics through the existing mercury entries (Schedule 2 for external therapeutic use with 0.5 per cent or less of mercury, Schedule 4 for other therapeutic uses). New Zealand subsequently agreed to this recommendation.

DISCUSSION - SUBMISSIONS

XXXXX identified that ARTG entries XXXXX for solutions containing 2 and 10 per cent merbromin, are listed as Schedule 2 medicines. By XXXXX calculation a 2 per cent solution of merbromin contains 0.534 per cent mercury and a 10 per cent solution of merbromin contains 2.67 per cent mercury, exceeding the permitted concentrations for Schedule 2. These figures were confirmed.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (e) dosage and formulation.

A Member noted that perhaps the 2 per cent solution of merbromin containing 0.534 per cent of mercury could be considered as Schedule 2 due to rounding. Other Members asserted that the amount mercury in a preparation should not be rounded down and the Schedule 2 cut-off of 0.5 per cent mercury should apply.

Members agreed to clarify that 2 and 10 per cent solutions of merbromin for therapeutic use are Schedule 4 unless specifically listed in Schedule 6 (topical treatment of animals).

The Committee also noted that the ARTG also lists an entry (XXXXX) for a 1 per cent merbromin solution (containing 0.27 per cent mercury) which was listed as Schedule 6.

RESOLUTION 2010/58 - 25

The Committee confirmed that the scheduling of mercurochrome for human therapeutic use is appropriately captured through the mercury schedule entries and agreed to convey this to the TGA and seek clarification.

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

No items.

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

16.1.1 CORIFOLLITROPIN ALFA

PURPOSE

The Committee considered the scheduling of corifollitropin alfa.

BACKGROUND

Corifollitropin alfa is a follicle stimulant produced by recombinant DNA technology with prolonged duration of follicle stimulating hormone (FSH) activity. Its prolonged activity was achieved by adding the carboxy-terminal peptide of the β-subunit of human chorionic gonadotropin to the β-chain of human FSH. Corifollitropin alfa has the ability to initiate and sustain multiple follicular growth for an entire week. A single subcutaneous injection of the recommended dose of the substance may replace the first seven injections of daily (recombinant) FSH preparations in a controlled ovarian stimulation treatment cycle.

At the May 1985 meeting, the Committee agreed to list follicular stimulating hormone (later listed as follicle stimulating hormone) in Schedule 4. At the November 1986 meeting, the Committee agreed to include specific listings for follicle stimulating hormones in Appendix D, paragraph 1. There was no record in the meeting minutes as to the reasons for the Appendix D classification.

At the November 1989 meeting, the Committee agreed to also list urofollitrophin (later harmonised as urofollitropin) in Appendix D, paragraph 1. At the August 1996 meeting, follitropin beta was included in Schedule 4 and Appendix D, paragraph 1. At the November 1997 meeting, follitropin alpha was added to Schedule 4 and Appendix D, paragraph 1.

At the June 2006 meeting, the Committee noted that the New Zealand (NZ) and Australian entries for FSH were currently harmonised, with specific entries for follitropin alfa, follitropin beta and urofollitropin.

DISCUSSION - SUBMISSIONS

At the November 2009 NZ Medicines Classification Committee (MCC) meeting, it was recommended that corifollitropin alfa be classified as a prescription medicine. It was noted that corifollitropin alfa (solution for injection, 100 micrograms / 0.5 mL and 150 micrograms / 0.5 mL) is a gonadotropin indicated for the treatment in controlled ovarian stimulation to induce the development of multiple follicles and pregnancy in women participating in an assisted reproductive technology programme. The substance has similar pharmacological features to FSH but different pharmacokinetic properties.

The Committee also noted from the Martindale monograph for human menopausal gonadotrophins, that the adverse side effects of FSH are the same as for human menopausal gonadotrophins and include dose-related ovarian hyperstimulation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock and thromboembolic disorders. Rupture of ovarian cysts and intraperitoneal haemorrhage has occurred, usually after pelvic examination. Fatalities have been reported. Hypersensitivity reactions and local reactions at the injection site may occur.

Members additionally noted that in November 2009, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive opinion recommending a marketing authorisation for corifollitropin alfa (100 micrograms / 0.5 mL, 150 micrograms / 0.5 mL, solution for injection) intended for the controlled ovarian stimulation in combination with a GnRH antagonist for the development of multiple follicles in women participating in an assisted reproductive technology program.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (c) potential hazards, (e) dosage and formulation, (f) need for access and (g) potential for abuse.

A Member asserted that as corifollitropin alfa has similar pharmacological features to FSH, it was adequately captured by the class entry for FSH and therefore Australia is essentially harmonised with NZ. Other Members asserted that as corifollitropin alfa has distinctive pharmacokinetic profile (sustained release), a specific entry would be more appropriate for clarity and consistency with previous entries for follitropin alfa, follitropin beta and urofollitropin.

A Member asserted that the weekly dosage regimen versus alternative daily FSH injections makes corifollitropin alfa more attractive to consumers and additional controls should be placed on its supply. Other Members also asserted that as corifollitropin alfa is likely to receive Australian registration approval in the future, an entry in Appendix D paragraph 1 is appropriate. Additionally, it was noted that an Appendix D, paragraph 1 listing would maintain consistency with the scheduling of follitropin alfa, follitropin beta and urofollitropin.

RESOLUTION 2010/58 - 26

The Committee decided to harmonise with New Zealand and include specific entries for corifollitropin alfa in Schedule 4 and Appendix D, paragraph 1.

Schedule 4 – New entry

CORIFOLLITROPIN ALFA.

Appendix D, Paragraph 1 – New entry

CORIFOLLITROPIN ALFA (recombinant follicle stimulant) for human use.

16.1.2 FAMCICLOVIR

PURPOSE

The Committee considered the scheduling of famciclovir.

BACKGROUND

Famciclovir, a synthetic guanine derivative, is the oral form of penciclovir. Famciclovir is rapidly converted in vivo into penciclovir, which has in vitro activity against herpes simplex viruses and the varicella zoster virus. Penciclovir targets virus-infected cells where it is rapidly converted into penciclovir triphosphate (mediated via virus-induced thymidine kinase). The triphosphate inhibits viral DNA polymearase competitively with deoxyguanosine triphosphate. Consequently, viral DNA synthesis and therefore, viral replication are inhibited. This triphosphate persists in infected cells in excess of 12 hours. The long intracellular half-life of penciclovir triphosphate ensures prolonged antiviral activity.

At the May 1995 meeting, the Committee considered the scheduling of famciclovir for the treatment of herpes zoster infection and decided to include famciclovir in Schedule 4.

At the February 2009 meeting the Committee rejected the down-scheduling of famciclovir for the treatment of herpes labialis (cold sores) in immunocompetent patients from Schedule 4 to Schedule 3 with inclusion in Appendix H. The down-scheduling of famciclovir was again considered at the October 2009 meeting, however, on this occasion inclusion in Appendix H was not sought. The Committee again decided that Schedule 4 remained appropriate.

At the May 2009 New Zealand Medicines Classification Committee (MCC) meeting, the MCC rejected a submission for the reclassification of famciclovir 500 mg tablets from prescription medicine to restricted medicine in packs of three tablets for the treatment of recurrent herpes labialis. However, the MCC agreed to review the submission if further

information on warnings and training material relating to use in immunocompromised patients was provided.

DISCUSSION – SUBMISSIONS

Members noted that it was becoming more common for sponsors to initiate parallel submissions to both NDPSC and MCC. Given the different timetables for NDPSC and MCC this could, as was the case here, result in either committee making a decision on a submission prior to (and potentially different from) the other. Members noted that the October 2009 NDPSC decision on famciclovir had not yet been considered by the MCC.

November 2009 MCC consideration

At its November 2009 meeting, the MCC reconsidered the May 2009 request to reclassify famciclovir as additional supporting information had been provided by the applicant. The MCC concluded that famciclovir 500 mg tablets could be reclassified from prescription to restricted medicine when sold in packs of three tablets for the treatment of recurrent herpes labialis, provided Medsafe was satisfied that:

- the applicant had approached the Pharmaceutical Society requesting their input on the treatment algorithm and implemented any suggested changes; and
- a warning that treatment should not be repeated within seven days is included.

The MCC noted that the applicant also proposed the following warning statements be added to the pack:

- Caution: If you have kidney disease check with your doctor or pharmacist before commencing treatment; and
- Not recommended for patients under 18 years of age.

The MCC additionally noted that the applicant's revised submission also proposed three other changes:

- to market the product as Famvir ONCE which would help reinforce the single dose concept;
- to supply every pharmacy with a training kit; and
- to develop patient education material aimed at making patients aware of the optimal time to treat cold sores and to speak to their pharmacist about all treatment options.

The MCC also noted that the applicant had developed a treatment algorithm designed to help pharmacists identify patients who might benefit from the appropriate cold sore therapy and to screen out patients who were unsuitable for over-the-counter (OTC) treatment, for example patients who may have impaired renal function or may be immunocompromised.

The MCC noted that, while pharmacists may not always know if a person had renal impairment, if there was renal impairment present accumulation would not occur from a single dose of famciclovir. The MCC also noted that some other medicines available without prescription used in multiple doses also have a caution for renal impairment.

Pre-meeting submissions

XXXXX provided a pre-meeting submission in support of harmonising with the MCC's decision. The submission also provided additional information addressing specific matters under 52E which were raised in the minutes of the October 2009 meeting (more details below):

- In relation to the lack of data reporting resistance, the submission referred to two Griffiths 2009 publications: Griffiths, PD. (2009[1], pre-publication manuscript) Perspective on the incidence of strains of herpes Simplex Virus resistant to acyclovir or penciclovir XXXXX; and Griffiths, PD. (2009[2]) A perspective on antiviral resistance. *Journal of Clinical Virology 46*:3-8. The submission stated that lab studies had searched for resistance and shown that incidence had not increased since the licensure of aciclovir/penciclovir and most cases of failure to respond to treatment were due to the patients' underlying impaired immune functions. The submission also stated that XXXXX conducts routine pharmacovigilance for any increase in resistance to famciclovir.
- In relation to the lack of testing of resistance in the general population, the submission referred to the XXXXX for famciclovir which state that clinical experience does not show emergent resistance to penciclovir in immunocompetent individuals despite prolonged periods of treatment. The submission also again referred to Griffiths, 2009[1] stating further drug exposure will not result in the increase of future incidences of resistance.
- In response to the issue that a lack of evidence of resistance is not the same as evidence of no resistance, the submission stated that it was unreasonable to expect evidence to prove that resistance will not change following OTC availability. The submission instead again referred to Griffiths, 2009[1] stating that due to rates of resistance remaining static following the widespread use of famciclovir, further development of resistance was unlikely.
- In relation to the efficacy of single versus multi-dose preparations, the submission referred to XXXXX stating that acceptable efficacy and safety had been demonstrated in both single and multi-dose regimens.
- In response to whether famciclovir was more beneficial than existing topical treatments, the submission stated that famciclovir was offered as an alternative to topical therapy and that according to the Interim Guidelines for the NDPSC, benefit of a therapy over existing therapies was not a requirement for down-scheduling. The submission also stated that the convenience of famciclovir's single oral dosage would result in significant public benefit over multiple topical applications.

- In relation to the efficacy of single vs multidose therapy in immunocompromised patients, the submission clarified that treatment was intended for immunocompetent individuals only. It recommended that warning labels be included specifying that famciclovir not be used by children, adolescents or patients with impaired kidneys or immune systems.
- The submission highlighted that an entry in Appendix H for famciclovir was not appropriate.

XXXXX also provided a pre-meeting submission in support of harmonising with the MCC's decision, stating that if Schedule 3 listing were to be granted, XXXXX would work in partnership with the applicant to facilitate the development of a protocol and other practice support tools for pharmacists to facilitate appropriate access to consumers in the community pharmacy setting including the prevention of off-label use.

XXXXX opposed harmonising with the MCC's decision and believed the current scheduling arrangements for famciclovir in Australia was appropriate.

Previous consideration at the October 2009 NDPSC meeting

At the October 2009 meeting, XXXXX submitted an application requesting the same famciclovir down-scheduling as currently proposed. Although the evaluator supported the application for down-scheduling, the Committee confirmed the current scheduling of famciclovir as Schedule 4. Reasons for this decision included:

- there was insufficient evidence of the efficacy of single oral dose vs. multi-day oral dose for herpes labialis in immunocompromised patients and Members stated it would be unrealistic to expect a pharmacist to dose-adjust famciclovir for immunocompromised patients and patients with renal impairment in a non-hospital setting;
- the benefit of oral treatment over topical therapy was not significant in the general population and there was merit in first treating herpes labialis topically and reserving oral treatment as a second line therapy; and
- there was limited data on resistance to famciclovir in the community and down-scheduling did not reflect a good risk vs. benefit ratio. It was noted that virus resistance was normally tested in immunocompromised patients and may not have been specifically tested in the broader population. The Committee required additional information on the issues of possible increase in resistance through wider community use and the implications of off-label use (eg. for genital herpes).

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards and (f) need for access.

The Committee revisited in detail the issue of resistance. A Member asserted that as famciclovir is a prodrug of acyclovir (a Schedule 4 substance except in single preparations for the treatment of herpes labialis where the risk of development of resistance is low) the propensity for resistance to famciclovir was unlikely. Members also noted the pre-meeting submission's claims that regular pharmacovigilance of resistance was being conducted. However, a Member asserted that pharmacovigilance would be unlikely to detect resistance and a lack of therapeutic effect could be associated with individual patient qualities rather than resistance. Another Member noted that the potential for resistance to famciclovir was previously assessed by XXXXX with favourable results.

The Committee also considered the potential benefits of harmonising with the MCC famciclovir decision. A Member noted that, with access to GPs restricted in some communities, a Schedule 3 listing would assist in both facilitating immediate action to reduce infection and improving treatment compliance. Several Members further asserted that any reduction in infection also had a broader benefit in reducing subsequent infectivity in the general population. A Member also noted that Schedule 3 supply of famciclovir requires the involvement of a health professional which the Member asserted would be adequate to maintain the integrity of famciclovir use as a second line treatment. A Member additionally asserted that the risk vs. benefit profile of famciclovir is similar to that of aciclovir.

Other Members, however, contended that the benefit arguments were less convincing since it had not been established that the proposed famciclovir treatment had greater efficacy than existing treatments. Several Members disagreed with the argument in the pre-meeting submission that efficacy over existing treatments was not a requirement for down scheduling. While there seems to be a genuine need for some Schedule 3 systemic treatment, these Members asserted that demonstrated efficacy was a central pillar for any argument claiming improved benefit to public health.

Members also considered whether the concerns from the October 2009 consideration had been sufficiently addressed so as to support harmonisation with the MCC decision.

In particular, there was a detailed consideration of the arguments put forward in the pre-meeting submission. Several Members asserted that the pre-meeting submission had provided further information appropriately addressing the concerns raised by the Committee during its October 2009 consideration. Other Members contended that, while expanding somewhat on the arguments considered at the October 2009 meeting, there was no substantially new robust information that would allay the concerns raised at that time.

Members additionally noted that the MCC had not had the opportunity to consider the October 2009 NDPSC minutes prior to their decision on famciclovir. A Member also asserted that while harmonisation between NZ and Australia was a objective, it was not a requirement. Several Members also contended that the MCC's decision to down schedule famciclovir was dependant on a number of NZ specific requirements (including

development of an appropriate treatment algorithm), and argued that Australian jurisdictions may not be able to enforce these requirements to a similar degree.

RESOLUTION 2010/58 - 27

The Committee noted that the New Zealand and Australian entries will not be harmonised.

16.1.3 FEXOFENADINE

PURPOSE

The Committee considered the scheduling of fexofenadine.

BACKGROUND

Fexofenadine is an orally active non-sedating histamine H1-receptor antagonist used in the symptomatic relief of allergic conditions including seasonal allergic rhinitis (SAR) and chronic urticaria. Fexofenadine is the carboxylic acid metabolite of terfenadine.

At the May and August 1996 meetings, the Committee considered a request to initially schedule fexofenadine as per terfenadine (Schedule 3). It was agreed that as there was insufficient evidence to make a decision in regard to the toxicity of fexofenadine, a Schedule 4 entry was appropriate at that time. This scheduling was reconsidered at the November 1996 meeting, where the Committee noted additional safety data, and decided that the oral divided preparations of fexofenadine should be included in Schedule 3.

At the February 1997 meeting, the Committee considered a post-meeting request for a temporary Schedule 4 entry for all pack sizes so that the initial availability of fexofenadine would be under greater control. However, the Committee noted that a major reason for its November 1996 Schedule 3 decision was that it had been satisfied that the available evidence indicated that fexofenadine was a safer drug than the prodrug, terfenadine. The Committee agreed that the decision to include fexofenadine as Schedule 3 remained appropriate.

At the August 1998 meeting, the Committee agreed that it was appropriate for fexofenadine to be included in Appendix H.

At the November 1998 and February 1999 meetings, following recommendations from the Trans-Tasman Harmonisation Working Party, the Committee agreed to reschedule fexofenadine from Schedule 3 to Schedule 2. The New Zealand and Australian entries for fexofenadine were then harmonised at the November 1999 meeting.

At the October 2009 meeting, the Committee considered a request to exempt oral fexofenadine from scheduling for the short term treatment of SAR, deferred from the

June 2009 meeting. The Committee decided that the current scheduling of fexofenadine (Schedule 2) remained appropriate.

DISCUSSION - SUBMISSIONS

Members noted that it was becoming more common for sponsors to initiate parallel submissions to both NDPSC and MCC. Given the different timetables for NDPSC and MCC this could, as was the case here, result in either committee making a decision on a submission prior to (and potentially different from) the other. Members noted that the October 2009 NDPSC decision on fexofenadine had not yet been considered by the MCC.

November 2009 MCC consideration

At its November 2009 New Zealand Medicines Classification Committee (MCC) meeting, the MCC considered the reclassification of fexofenadine hydrochloride from a pharmacy only medicine to a general sales medicine for the treatment of SAR.

The MCC recommended that capsules containing 60 mg or less and tablets containing 120 mg or less of fexofenadine hydrochloride should be classified as general sales medicines when:

- used only for short term treatment (maximum five days of therapy) of SAR;
- used in adults and children 12 years and over;
- used in small (maximum 10 dosage units) oral presentations with a maximum daily dose of 120 mg; and
- sold in packs approved by the Minister or the Director-General for distribution as a general sales medicine.

The MCC also recommended that a warning statement be included on the pack to the effect of:

- do not use with other anti-histamines; and
- this product should not be used when pregnant or when breast feeding except when advised by your Doctor or Pharmacist.

The MCC discussed the issues surrounding SAR self diagnosis and the impact of supermarket availability on use of fexofenadine during pregnancy and for indications other than SAR. The MCC agreed that these issues could be addressed by appropriate labels.

Pre-meeting submissions

XXXXX opposed the proposal and reiterated XXXXX comments made for the October 2009 meeting, noting that while the condition could be easily recognised by consumers

and was suitable for short-term self-treatment, there were instances when professional intervention was necessary at the time of supply.

XXXXX agreed with the October 2009 decision, stating that all preparations for oral use containing fexofenadine should remain as Schedule 2, thereby ensuring that pharmacist advice would be available if necessary.

XXXXX recommended that fexofenadine remain as currently scheduled, stating that:

- with greater availability and a lack of attention to label warnings the risks of pregnant or breast feeding mothers taking fexofenadine would increase;
- access to fexofenadine was currently adequate as pharmacy opening hours were extensive;
- as there was currently extensive competition with other less sedating antihistamines already within the pharmacy market, the consumer would not benefit from reduced prices; and
- as treatment is dependant on the type of rhinitis, pharmacists are trained to differentiate between allergic rhinitis (seasonal and perennial) and non-allergic rhinitis (including drug-induced, hormonal, structural and occupational) and recommend the most appropriate therapy.

Previous consideration at the October 2009 NDPSC meeting

Members noted previous discussion at the October 2009 meeting on the effectiveness and limited adverse side effects of fexofenadine, as well as the low potential for abuse. Members also noted that at the October 2009 meeting the Committee decided to reject the application to exempt fexofenadine, noting:

- the evaluator's recommendation that the re-scheduling proposal be rejected due to concerns over the safety of use in pregnant or breast-feeding women and to the inaccuracy of SAR self-diagnosis;
- that the benefit from access to fexofenadine out-of-hours would not outweigh the central safety concerns relating to use during pregnancy and that it would be inappropriate to try and address these pregnancy concerns solely through label warnings; and
- a pre-meeting submission stating that with wider availability and lack of advice at the time of purchase there could be an increase in the incidence of adverse drug reactions.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (b) risks and benefits and (f) need for access.

The Committee noted that no substantially new information addressing the concerns raised at the October 2009 meeting had been received. There were a number of pre-meeting submissions, but these all essentially reiterated arguments raised previously.

Members discussed the need for access to fexofenadine for treating SAR and whether this was a significant issue under the current Schedule 2 access restrictions. A Member asserted that the removal of scheduling would ensure access in situations where SAR symptoms occur unexpectedly (e.g. in different seasons or while travelling). Other Members suggested that the pharmacy opening hours were now extensive and asserted that access was already adequate, noting that there were existing jurisdictional arrangements to allow access to Schedule 2 medicines in those areas with limited access to a pharmacy.

Members also again considered the concern regarding the inaccuracy of SAR self-diagnosis. A Member asserted that in those (not infrequent) cases where a cold is misdiagnosed as SAR, the risks from use of fexofenadine were minimal. Other Members contended, however, that this remained a concern and was a reason to retain the current Schedule 2 fexofenadine entry, to ensure that pharmacists advice would be available if necessary, particularly where someone was unsure of their SAR self-diagnosis..

Members additionally revisited the October 2009 concern regarding use during pregnancy. Several Members asserted that any such concern could be handled adequately by labelling, consistent with some other unscheduled substances. These Members particularly noted the general sales availability of fexofenadine overseas and the lack of evidence of safety when used during pregnancy. Other Members, however, reiterated the October 2009 conclusion that it would be inappropriate to try and address these pregnancy concerns solely through label warnings. One Member asserted that, when considering this risk it was not sufficient to only consider the pregnancy classification. The Member gave the example of general sale aspirin which has a similar pregnancy classification but, unlike the uncertainty with fexofenadine, for aspirin the pregnancy risk was largely confined to the end of pregnancy. The Member was particularly concerned that people could be using fexofenadine in early pregnancy (when they do not realise they are pregnant), given the current lack of knowledge with regard to possible adverse effects from fexofenadine use in these cases. Other Members contended that this concern should not carry a lot of weight given the much greater risk posed by other medicines (not to mention alcohol or smoking) people could routinely be using in early pregnancy when they were not aware they were pregnant.

RESOLUTION 2010/58 - 28

The Committee noted that the New Zealand and Australian entries for fexofenadine were not harmonised.

16.1.4 HEPARINS

PURPOSE

The Committee considered the scheduling of heparins.

BACKGROUND

Heparins are anionic polysaccharides of mammalian origin with irregular sequence. They consist principally of alternating iduronate and glucosamine residues, most of which are sulfated. They may be described as a sulfated glucosaminoglycan. Heparins have the characteristic property of delaying the clotting of freshly shed blood. They may be prepared from the lungs of oxen or the intestinal mucosa of oxen, pigs, or sheep. Heparins are often described in the literature as standard heparins or unfractionated heparins to distinguish them from low-molecular-weight heparins that consist of only short chains of polysaccharide.

Heparin was first considered by the Committee at its November 1963 meeting. The Committee agreed that heparin be scheduled in Schedule 4 and further agreed that anticoagulant substances for external application did not warrant scheduling.

At the October 2006 meeting, the Committee noted a number of recommendations from the Trans Tasman Harmonisation Working Party, including the proposal that Australia harmonise with NZ and replace 'heparin' with 'heparins'. The Committee agreed to this clarification and also supported the approach of separately listing low molecular weight heparins.

Low molecular weight heparins, including dalteparin, enoxaparin, logiparin, nadroparin and tinzaparin, are currently listed under Schedule 4.

Additionally, Appendix A includes a general exemption for a number of blood products, and this exemption would apply regardless of whether or not a heparin was present.

DISCUSSION - SUBMISSIONS

At the November 2009 MCC meeting, it was recommended that the existing prescription classification for heparins be amended to exempt heparin when present as an excipient. The following was noted:

- At the November 2008 MCC meeting, blood and blood products were recommended for reclassification as general sales medicines with the intention of harmonising with Australia. An unintended consequence of this had been identified; some products containing blood clotting factors also contained small amounts of heparin as an excipient. Heparins remain classified as a prescription medicine, thereby preventing these products from being reclassified to general sale in NZ as had been the intention.

- The MCC noted that a similar exemption had been used in the past to exempt phenacetin when used as an excipient. The NDPSC decision to harmonise with NZ with regard to an exemption for excipient phenacetin was made at the February 2000 meeting.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (d) extent and patterns of use and (h) purpose of use.

The Committee discussed the differences in scheduling between NZ and Australia in relation to heparins. A Member noted that in Australia, if a blood product qualified for the Appendix A general exemption then that product remained exempt from scheduling regardless of the presence of heparins. The Member asserted that due to the differences in scheduling structure, the NZ and Australian entries for heparins were already essentially harmonised.

Members also discussed the potential unintended consequences of exempting heparins as an excipient. A Member asserted that the proposed exemption could inadvertently exclude heparins for other uses (besides use in blood products) from scheduling. Another Member also asserted that the proposed exemption may have unforseen effects on access to heparins in relation to a compounding pharmacy setting, specifically where the facilities provide compound products containing heparins on prescription. Although Members noted that a search of the ARTG indicated that the only products using heparins as excipients were blood products, a Member asserted that compound products may not be listed by the TGA.

Members generally agreed that there were numerous potential unintended consequences of exempting heparins as an excipient and, due to the Appendix A general exemption, the current scheduling of heparins ensured appropriate access.

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The Committee decided that the current scheduling of heparins remained appropriate, and that Australia was essentially harmonised with NZ with regard to heparins.

16.1.5 IBOGAINE AND NORIBOGAINE

PURPOSE

The Committee considered the scheduling of ibogaine and its metabolite noribogaine.

BACKGROUND

Ibogaine, an indole alkaloid, is obtained from the root of the West African shrub, Tabernanthe iboga (*Apocynaceae*). Ibogaine has been used to treat both drug (e.g.,

heroin, methadone, cocaine) and alcohol dependency. Ibogaine inhibits cholinesterase, leading to the accumulation of synaptic acetylcholine and cholinergic hyperactivity (slowing of the heart rate, hypotension, convulsions, paralysis, and respiratory arrest). The pharmacologic effects (CNS stimulation - mild excitation, euphoria, visual and auditory hallucinations) are usually dose-dependent. It has been suggested that a single administration of ibogaine has the ability to either prevent or ameliorate the symptoms of drug withdrawal and reduce drug craving.

DISCUSSION - SUBMISSIONS

At the November 2009 New Zealand Medicines Classification Committee (MCC) meeting, the MCC considered the scheduling of ibogaine following the receipt of enquiries on the import of ibogaine into New Zealand. The MCC recommended the classification of ibogaine and its metabolite noribogaine as prescription medicines and noted the following:

- the use of ibogaine for the treatment of drug dependence had been based on anecdotal reports from American and European addict self-help groups that it decreased the signs of opiate withdrawal and reduced drug craving for cocaine and heroin for extended periods;
- currently, the pharmacological targets underlying the physiological and psychological actions of ibogaine are not completely understood; and
- the purported efficacy of ibogaine following single-dose administrations may be due to the formation of an active metabolite (ibogaine is o-demethylated to 12-hydroxyibogamine [noribogaine] by the activity of liver enzymes). As noribogaine appears to have a slow clearance rate in humans, this suggests that some of the after effects of ibogaine may be due to the actions of the metabolite.

The MCC based its decision on:

- the need for supervision of the substances' use in the management / treatment of addiction to limit attempts at self treatment and prevent recreational use as a "party pill" (although noting that the documented experience is usually not pleasant);
- the need to control the import and supply of ibogaine, its metabolite or products containing each or both of the substances;
- data suggesting that the number of deaths due to ibogaine were lower than those associated with methadone; and
- opinion that although ibogaine's appeal as a recreational drug was low, there were dangers in *ad hoc* use as a self medication for drug addiction following potential media interest.

Other considerations

According to the Poisindex monograph for ibogaine, ibogaine was generally well tolerated – nausea, vomiting, ataxia, and mild tremor were the most frequent side effects reported. Reports of bradycardia, hypotension, heart failure, seizures, paralysis, and respiratory arrest have also been associated with ibogaine therapy. Ingestion of large amounts may induce hallucinations and cause both anxiety and apprehension. Deaths have been associated with ibogaine treatment doses of 20 mg / kg or higher, however, there was inadequate data to determine if ibogaine was the cause. Theoretically, concurrent use of ibogaine and cholinergic agents may increase cholinergic adverse effects.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (f) need for access and (g) potential for abuse.

A Member suggested that both ibogaine and noribogaine warranted control through inclusion, at the least, in Schedule 4. There was discussion, however, whether controls should in fact be tighter (i.e. Schedule 8 or Appendix D). A Member asserted that misuse for the hallucinogenic effect would be somewhat limited due to the reported unpleasant nature of this effect. Another Member noted that, while these were dangerous drugs linked with deaths, these deaths were largely associated with unsupervised use (due often to actions while in a hallucinating state).

A Member also advised that use of these substances was not new, with occasional interest over the years for legitimate use (somewhat limited as this was by the unpleasant common side effects such as nausea and vomiting). Members noted that there was currently renewed Australian and international interest in the use of ibogaine and noribogaine, with a number of studies either planned or underway (mostly with regard to use as a treatment for drug dependency).

Members generally agreed that Schedule 4 was the appropriate level of control in balancing the misuse concerns against the need for professional access (without the added burden of Schedule 8 controls) for research and supervised clinical trials. Members also agreed that, as there was no registered product, the current TGA restrictions on importing and accessing unregistered medicines were sufficient and there was no need for additional controls through an Appendix D listing.

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The Committee decides to harmonise with New Zealand and include new entries for ibogaine and noribogaine in Schedule 4

Schedule 4 - New entries

IBOGAINE.

NORIBOGAINE.

16.1.6 LANSOPRAZOLE

PURPOSE

The Committee considered the scheduling of lansoprazole.

BACKGROUND

Lansoprazole is a proton pump inhibitor (PPI) similar to omeprazole (Schedule 4) and rabeprazole and pantoprazole (both Schedule 3 and Schedule 4). It binds irreversibly to the proton pump on the mucosal membrane of the gastric parietal cells which inhibits gastric acid secretion, reduces the pH of the gastric fluid, and thus reduces the pain associated with the reflux of gastric fluid into the lower oesophagus. The inhibitory effect is dose-related.

Lansoprazole was first considered in April 1994 meeting, when it was included in Schedule 4.

At the February 2003 meeting, the Committee rejected a proposal to reschedule 30 mg oral lansoprazole from Schedule 4 to Schedule 3, for the relief of symptoms of gastro-oesophageal reflux disease (GORD) (heartburn) and acid-related dyspepsia (indigestion). The Committee noted that safety data for OTC use for wider indications including GORD and dyspepsia, and evidence of efficacy for these indications, were not properly addressed.

At the June 2003 meeting, the Committee reconsidered the above proposal following provision of new data by the applicant. The Committee concluded that the data submitted were not adequate to support the proposed use of lansoprazole in Schedule 3.

Recent Scheduling of other PPIs

Pantoprazole was rescheduled from Schedule 4 to Schedule 3 at the June 2005 meeting for the relief of heartburn and other symptoms of GORD in oral preparations containing 20 mg or less, in packs containing not more than 14 days supply. At the February 2009 the Committee reject a proposal to include pantoprazole in Appendix H (for more details please refer to item 12.2.2 Pantoprazole of this meeting).

Rabeprazole was rescheduled from Schedule 4 to Schedule 3 at the June 2009 meeting for oral preparations containing 10 mg or less of rabeprazole for the relief of heartburn and other symptoms of GORD, in packs containing not more than 14 days supply.

The scheduling of omeprazole was also considered at this meeting (item 16.1.7).

DISCUSSION - SUBMISSIONS

At the November 2009 NZ Medicines Classification Committee (MCC) meeting it was recommended that tablets or capsules containing 15 mg or less of lansoprazole be reclassified from prescription to restricted medicine. The following was noted:

- This reclassification had been previously rejected by the MCC at its November 2008 meeting. The MCC had been reasonably satisfied with the submission at that time but noted that appropriate warnings should be included on the pack and that further clarification was required regarding the efficacy of the proposed dose regimen.
- Additional information was subsequently provided which appeared to resolve the labelling and safety concerns. Nine references from the literature on the efficacy of 15 mg daily dosage were also provided. The data were derived from evidence of effect at 24 hours on intragastric pH and on interim analysis of 4 and 8 week studies following 14 days treatment, and so appeared to demonstrate efficacy in terms of symptom resolution.
- The MCC felt that although the applicant had not fully addressed its requests, there was no evidence to suggest that the risk benefit profile of lansoprazole 15 mg capsules would be significantly different from that seen for pantoprazole and omeprazole which had been reclassified as restricted medicine (for more details on omeprazole reclassification please refer to item 16.1.7 of this meeting).
- The MCC concluded that lansoprazole should be reclassified from prescription medicine to restricted medicine provided that similar requirements were met to those detailed for the OTC sale of both omeprazole and pantoprazole in the New Zealand Regulatory Guidelines for Medicines, as follows:

    a. it must be sold in the manufacture's original pack;
    b. the strength in each dose unit should not exceed 15 mg;
    c. the maximum daily dose should not exceed 15 mg;
    d. the pack size must not exceed 14 dose units;
    e. the indication should be limited to the relief of heartburn and short-term, symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and over;
    f. the following warning statements, or words of similar meaning, are required on the label:
        i. for short-term use only, except on medical advice
        ii. do not use the medicine for any purpose other than that specified on the pack, except on medical advice
        iii. do not use if you are experiencing weight loss, persistent regurgitation of food or vomiting, difficulty swallowing or symptoms of gastro-intestinal bleeding, except on medical advice

iv. consult a doctor if symptoms persist, recur or worsen or if new symptoms occur
v. consult a doctor or pharmacist before use if you are pregnant or are taking any other medicines; and

g. the package insert should include all interactions specified on the data sheet.

Pre-meeting Submissions

XXXXX supported the down-scheduling of 15 mg or less of lansoprazole for the relief of heartburn and other symptoms of GORD, from Schedule 4 to Schedule 3, based on the safety profile of lansoprazole and the inclusion of similar PPI in Schedule 3.

XXXXX also requested that the applicant should provide any new evidence-based information on PPIs and GORD to the pharmacy profession so that the quality use of PPIs could be reinforced with consumers.

XXXXX did not support the inclusion of lansoprazole in Appendix H, as there was no data or information available in relation to its OTC use in Australia.

XXXXX asserted that while it did not believe that Australia should necessarily align with decisions from New Zealand if there were safety or efficacy concerns, in this instance it believed that lansoprazole had appropriate efficacy and safety profiles to be included in Schedule 3 for short-term treatment of heartburn and reflux. In addition, XXXXX provided comments with particular reference to section 52E, including:

(b) Risks and Benefits

- In a US evaluation of PPIs in 2000, it was concluded that PPIs were the drugs of choice for treating patients with acid-related GI diseases and that it could be anticipated that PPIs should all provide similar efficacy rates.
- The study identified that pantoprazole and rabeprazole had a lower drug interaction potential but emphasised that very few clinically important drug interactions had been reported despite the widespread use of lansoprazole.
- The study also identified that the adverse effects (AEs) for short-term use (less than 12 weeks) was similar to those of H2RAs such as ranitidine, being primarily headache, diarrhoea, constipation, nausea and pruritus. All PPIs appeared to have similar AE profiles with the short-term safety of lansoprazole being well established as these products have been available for a long period.

(f) Need for Access

- PPIs should be available for short-term relief of dyspepsia or gastric reflux under the direction and support of a pharmacist.

- Current professional guidelines for pharmacists about PPI use were specifically for pantoprazole. Generic supporting guidelines would be useful and XXXXX would be willing to collaborate with other organisations or companies to develop these.

In relation to Appendix H, XXXXX acknowledged some public benefit, however, it continued to have concerns about consumers requesting products based on a persuasive advertisement, particularly for new drug categories that were approved for Schedule 3 listing. However, it noted that pantoprazole had been available as a Schedule 3 item since May 2006, and that pharmacists were now familiar with PPI requests. As such, XXXXX believed that it was appropriate that any decision of the Committee for Appendix H listing of lansoprazole be consistent with that for omeprazole (item 16.1.7) and pantoprazole (item 12.2.2).

Adverse Effects

Members additionally noted the following from the Martindale monograph for lansoprazole:

- PPIs were generally well tolerated, and adverse effects were relatively infrequent. The adverse effects reported most often with lansoprazole and other PPIs were headache, diarrhoea, and skin rashes; they have sometimes been severe enough to require stopping treatment.
- Glossitis (associated in some cases with black tongue or stomatitis) has been reported in a few patients taking lansoprazole as part of a triple therapy regimen for *Helicobacter pylori* elimination in peptic ulcer disease. Discoloured tongue has also been reported in a patient taking lansoprazole alone.
- The incidence of diarrhoea might be greater with lansoprazole than omeprazole. Cases of microscopic colitis have been reported with use of lansoprazole. UK licensed product information stated that stopping therapy should be considered in the case of severe and/or persistent diarrhoea.

Previous NDPSC Considerations

Members recalled the following from the February and June 2003 considerations of down-scheduling lansoprazole (noting that the current proposal was for not more than 15 mg). The Committee rejected the proposal to down-scheduling for the following reasons:

- The data submitted were not considered adequate to support the proposed use of lansoprazole as an appropriate Schedule 3 medicine for intermittent, short-term treatment of the symptoms of heartburn and dyspepsia.
- The proposed indications for use, onset and duration of action were more appropriate for the prevention of symptoms rather than intermittent treatment of, or relief from, symptoms.
- There was no significant difference between the use of PPIs and histamine-2 receptor antagonists (H2RAs) in the treatment of heartburn for endoscopy-negative disease, which was more likely to represent the group of patients self-medicating. Members

noted that H2RAs including ranitidine, famotidine, nizatidine and cimetidine were currently available OTC.

- There was also an increased risk of masking more serious conditions if lansoprazole was taken as first-line treatment prior to medical assessment given the overlap in symptoms. Treatment with alternative therapies such as antacids, alginates or H2RAs might be appropriate in the first instance.
- The National Institute for Health and Clinical Excellence advised that patients with dyspepsia should not be treated with PPI's on a long-term basis without a definite clinical diagnosis being made by upper gastrointestinal endoscopy where appropriate.
- The Gastroenterological Society of Australia Guidelines stated that long-term PPI therapy in the presence of *H. pylori* infection increased the risk of gastric mucosal atrophy which was reduced by eradication therapy. As *H. pylori* infection and eradication therapy required medical intervention, the use of PPI's should not be advised prior to consultation with a doctor.

Members also recalled the following from the February and June 2009 pantoprazole and rabeprazole scheduling decisions which rejected listing in Appendix H:

- Pantoprazole inclusion in Appendix H was rejected by the Committee as there were insufficient data from Australian marketing to allow conclusions to be drawn on risks and benefits, potential hazards, extent and pattern of use and other relevant matters, in the context of advertising and public health benefit, as such, no conclusions on the likelihood of improvements in health outcomes could be drawn.
- Rabeprazole inclusion in Appendix H was rejected as the Committee was unconvinced that advertising of OTC rabeprazole would lead to greater public health benefits and there were concerns about the potential of 'inappropriate' use.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits, (d) extent and patterns of use, and (f) need for access to a substance.

XXXXX.

Members discussed the merits of the proposed Schedule 3 entry. It was noted that the concern that the applicant had not fully addressed the efficacy matters in terms of symptoms resolution, appeared to have been, at least partially, addressed by new information tabled at the November 2009 MCC meeting. Several Members also argued that the mode of action, safety profile and intended use pattern were relatively similar to other Schedule 3 PPIs (when for treating heartburn and other symptoms of GORD). The Committee generally agreed with the proposal for a Schedule 3 entry for lansoprazole.

Members then considered whether there was sufficient grounds for an Appendix H listing for lansoprazole. A Member asserted that the various PPIs in Schedule 3 appeared to be

sufficient similar that any decision regarding Appendix H should be consistent across the whole class. A number of Members asserted that the concerns raised regarding the request to list pantoprazole in Appendix H (item 12.2.2) would also apply to lansoprazole. Another Member noted that the market experience of OTC lansoprazole in Australia was limited at this time and asserted that allowing advertising would be inappropriate. The Committee generally did not support inclusion of lansoprazole in Appendix H.

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The Committee agreed to include lansoprazole in Schedule 3 when:

- in preparations containing 15 mg or less per dosage unit of lansoprazole for the relief of heartburn and GORD; and
- in a pack containing not more than 14 days of supply.

Schedule 3 – New entry

LANSOPRAZOLE in oral preparations containing 15 mg or less per dosage unit of lansoprazole 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

LANSOPRAZOLE – Amend entry to read:

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

16.1.7 OMEPRAZOLE

PURPOSE

The Committee considered the scheduling of omeprazole.

BACKGROUND

Omeprazole is a proton pump inhibitor (PPI). It suppresses secretion of gastric acid by inhibiting the enzyme system of hydrogen / potassium adenosine triphosphatase (H+/K+ ATPase), the ‘proton pump' of the gastric parietal cell. It is used in conditions where inhibition of gastric acid secretion may be beneficial, including aspiration syndromes, dyspepsia, gastro-oesophageal reflux disease (GORD) and peptic ulcer. Esomeprazole, a specific isomer of omeprazole, is also used for these conditions.

At the May 1989 meeting, the Committee agreed to the scheduling of omeprazole in Schedule 4.

At the November 2000 meeting, the Committee agreed to harmonise with the NZ classification of esomeprazole by including it in Schedule 4.

At the November 2001 meeting, the Committee considered a request to schedule omeprazole for the management of gastric ulcers in horses. Members agreed that this indication was appropriately captured by the existing Schedule 4 omeprazole entry.

The OTC availability of omeprazole 10 mg in NZ was decided by the Medicines Classification Committee (MCC) at its November 2008 meeting. This decision was not consequently considered by the NDPSC for harmonisation. It appears to have been overlooked.

The scheduling of other PPIs were also being considered at this meeting (pantoprazole item 12.2.2 and lansoprazole item 16.1.6).

DISCUSSIONS SUBMISSIONS

At the November 2009 MCC meeting it was recommended that tablets containing 20 mg or less of omeprazole be reclassified from prescription to restricted medicine for the short term relief of reflux-like symptoms. The following was noted:

- At the November 2008 meeting, the MCC recommended that tablets or capsules containing 10 mg or less of omeprazole should be reclassified to restricted medicine, based on additional information supplied by the applicant.
- The MCC discussed the possibility of patients misusing omeprazole 20 mg. It was noted that the packaging did not state to stop taking the product once symptoms had resolved. However, there was evidence of benefit associated with continued use for 14 days and other markets had approved the proposed dose regimen.
- The MCC recommended that that the label on the packaging of omeprazole 20 mg should include the following statement, or words of similar meaning '*do not take for more than 14 days; if symptoms persist, talk to your Doctor*'.
- An MCC pre-meeting comment noted that the complexity of the current restriction of 10 mg omeprazole (a dosage recommendation of two tablets taken initially each day until symptoms improve, then reduce to one daily, with a maximum pack size of 14 dosage units) could lead to a patient's non-compliance with the instructed regime. It was argued in the comment that a single daily dose of one 20 mg tablet (the current maximum restricted dose) for the full 14 day course would be more efficacious.

Pre-meeting Submissions

XXXXX opposed the down-scheduling of omeprazole 20 mg tablets and asserted that:

- The down-scheduling of the lowest effective doses of other PPIs (pantoprazole and rabeprazole), has only recently occurred in Australia. Pharmacist experience in recommending this class of medication was limited and remained to be assessed.

- Symptoms severity of GORD did not correlate with disease severity, and proper evaluation and treatment by a medical practitioner was essential for its management.
- GORD is a chronic relapsing disease. If left untreated, it can develop into erosive oesophagitis and other complications such as oesophageal strictures, oesophageal ulcers, Barrett's oesophagus and oesophageal carcinoma.

XXXXX supported the proposed down-scheduling of omeprazole based on the safety profile of omeprazole and the inclusion of similar PPIs in Schedule 3.

XXXXX proposed that lower doses of 10 mg per dosage unit of omeprazole, limited to 14 days supply, would be more appropriate for a Schedule 3 entry. It was noted that this would reflect the current pantoprazole and rabeprazole Schedule 3 entries, i.e. the strength which was equivalent to half the 'standard' dose.

XXXXX also requested that the applicant provided any new evidence-based information on PPIs and GORD to the pharmacy profession so that the quality use of PPIs could be reinforced with consumers.

XXXXX did not support the inclusion of omeprazole in Appendix H. XXXXX noted that there was no data or information available in relation to its OTC use in Australia.

XXXXX asserted that while not believing that Australia should necessarily align with decisions from NZ if there were safety or efficacy concerns, in this instance XXXXX believed that omeprazole had appropriate efficacy and safety profiles to be included in Schedule 3 for short-term treatment of heartburn and reflux. In addition, comments were provided with particular reference to section 52E, including:

(b) Risks and Benefits

- In a US evaluation of PPIs in 2000, it was concluded that PPIs were the drugs of choice for treating patients with acid-related GI diseases and that it could be anticipated that all PPIs should provide similar efficacy rates.
- The study identified that pantoprazole and rabeprazole had a lower drug interaction potential but emphasised that very few clinically important drug interactions had been reported despite the widespread use of omeprazole.
- The study also identified that the adverse effects (AEs) for short-term use (less than 12 weeks) was similar to those of H2RAs such as ranitidine, being primarily headache, diarrhoea, constipation, nausea and pruritus. All PPIs appeared to have similar AE profiles with the short-term safety of omeprazole being well established as these products have been available for a long period.
- Rare adverse drug reactions included hyponatraemia and interstitial nephritis, however, such reactions could occur with PPIs in general.

(f) Need for Access

- PPIs should be available for short-term relief of dyspepsia or gastric reflux under the direction and support of a pharmacist.

(g) Purposes for use

- Current professional guidelines for pharmacists about PPI use are specifically for pantoprazole. Generic supporting guidelines would be useful and XXXXX would be willing to collaborate with other organisations or companies to develop these.
- Acknowledged some public benefit relating to Appendix H, however, it continued to have concerns about consumers requesting products based on a persuasive advertisement, particularly for new drug categories that were approved for Schedule 3 listing. However, it noted that pantoprazole has been available as a Schedule 3 item since May 2006, and that pharmacists were now familiar with PPI requests. As such, it believed that it was appropriate that any decision of the Committee for Appendix H listing of omeprazole be consistent with that for lansoprazole (item 16.1.6) and pantoprazole (item 12.2.2).

Omeprazole worldwide

Members noted that omeprazole was available as OTC in countries such as:

- Sweden since April 2000: omeprazole 10 mg and 20 mg for 14-day treatment of GORD symptoms of heartburn and regurgitation.
- The US since June 2003: omeprazole 20 mg for 14-day treatment of frequent heartburn with a maximum of three courses per year. The US labelling for OTC omeprazole 20 mg advised consumers to see their doctor before using this product beyond the recommended 14-day treatment course.
- The UK since March 2004: omeprazole 10 mg, maximum 20 mg per day for up to four weeks, for reflux-like symptoms (heartburn). Omeprazole was available as a P (Pharmacy) medicine if the following conditions were met:

  (e) For the relief of reflux-like symptoms such as heartburn;

  (f) for adults aged 18 years and over;

  (g) for a maximum period of 4 weeks;

  (h) maximum strength: 10 mg;

  (i) maximum dose: 20 mg;

  (j) maximum daily dose: 20 mg; and

  (k) maximum pack size: 28 tablets.

  (l) Additionally the following information were required:

  - The Summary of Product Characteristics and leaflet should advise that the product will not give immediate relief.

- The product should not be taken with another acid-suppressor.
- If continuous treatment for more than 4 weeks is required to relieve symptoms, then the patient should be referred to a doctor.
- If no relief is obtained after 2 weeks, the patient should consult a doctor.

Adverse Events (AEs)

The Committee recalled that at the May 1989 meeting the major safety concern of omeprazole (a new drug at that time) arose from the preclinical evaluation which highlighted the development of gastric carcinoids in rats dosed with omeprazole for 2 years, and associated findings of ECL cell hyperplasia and gastric mucosal hypertrophy.

Members also noted the following from the Martindale monograph for omeprazole:

- Common reported AEs with omeprazole and other PPIs have been headache, diarrhoea, and skin rashes; they have sometimes been severe enough to require stopping treatment. Other effects included pruritus, dizziness, fatigue, constipation, nausea and vomiting, flatulence, abdominal pain, arthralgia and myalgia, urticaria, and dry mouth. Isolated cases of photosensitivity, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred.
- Effects on the CNS included occasional insomnia, somnolence, and vertigo; reversible confusional states, agitation, depression, and hallucinations have occurred in severely ill patients.
- Raised liver enzymes and isolated cases of hepatitis, jaundice, hepatic failure and hepatic encephalopathy, have been reported.
- PPIs may increase the risk of gastrointestinal infections because of their acid suppressive effects.

Incidence of AEs

- Monitoring for 16,205 patients prescribed omeprazole, 17,329 prescribed lansoprazole, and 11,541 prescribed pantoprazole indicated that AEs were reported infrequently, with the most common being gastrointestinal disturbances and headache. The incidences of diarrhoea, the most commonly reported event were 0.18 for omeprazole, 0.39 for lansoprazole, and 0.23 for pantoprazole. The apparent evidence of lansoprazole might be associated with a somewhat greater risk of diarrhoea, particularly in the elderly.

Drug Interaction

- Studies in healthy subjects had indicated that use of omeprazole with clarithromycin resulted in an approximate 30 per cent increase in peak plasma concentrations of omeprazole. Plasma concentrations of clarithromycin were also modestly increased,

as were local concentrations in gastric tissue and mucus. The interaction may contribute to the benefits of combined therapy for *Helicobacter pylori* infection.

- PPIs should not be used with clopidogrel. It may reduce its antiplatelet effect if patients were given a PPI with clopidogrel. Patients taking clopidogrel for cardiovascular indications have also shown an increase in cardiovascular events in those taking PPIs.
- The Medicines and Healthcare products Regulatory Agency in the UK and the EU Committee for Medicinal Products for Human Use have recommended that use of any PPI with clopidogrel be discouraged unless absolutely necessary. The USFDA had similarly advised that the need for starting or continuing a PPI be re-evaluated in patients taking clopidogrel.
- When omeprazole is given with voriconazole, exposure to both drugs is increased. The information for voriconazole stated that, while no dosage adjustment was considered necessary for voriconazole, when patients already receiving omeprazole were started on voriconazole, the dose of omeprazole should be halved. Other PPIs may be similarly affected by voriconazole.
- Dose reductions may need to be considered in patients treated with fluvoxamine and PPIs. Fluvoxamine increased exposure to omeprazole, lansoprazole, and rabeprazole in patients who were extensive metabolisers.
- There are reports noting that competitive inhibition of intestinal CYP3A4 by omeprazole might affect the first-pass metabolism of a number of drugs, including diazepam, phenytoin, and warfarin. A review concluded that, while omeprazole and possibly esomeprazole had a considerable potential for drug interactions, lansoprazole, pantoprazole and rabeprazole were associated with a lower incidence of drug interactions.
- Omeprazole may be used at high doses to prolong the action of central stimulants by inhibiting their metabolism.

Appendix H for other PPIs

Members also recalled the following from the February and June 2009 pantoprazole and rabeprazole scheduling decisions which rejected listing in Appendix H:

- Pantoprazole inclusion in Appendix H was rejected by the Committee as there were insufficient data from Australian marketing to allow conclusions to be drawn on risks and benefits, potential hazards, extent and pattern of use and other relevant matters, in the context of advertising and public health benefit, as such, no conclusions on the likelihood of improvements in health outcomes could be drawn.
- Rabeprazole inclusion in Appendix H was rejected as the Committee was unconvinced that advertising of OTC rabeprazole would lead to greater public health benefits and there were concerns about the potential of inappropriate use.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) risks and benefits, and (f) need for access.

Members discussed the merits of the proposed Schedule 3 entry. Several Members reiterated arguments from the lansoprazole consideration (item 16.1.6) that the mode of action, safety profile and intended use pattern were relatively similar to other Schedule 3 PPIs (when for treating heartburn and other symptoms of GORD). The Committee generally agreed with the proposal for a Schedule 3 entry for omeprazole.

Members then considered whether the Schedule 3 omeprazole entry should limit the dosage unit to 10 mg, consistent with the other Schedule 3 PPIs entries (i.e. the strength equivalent to half the 'standard dose') or whether the entry should harmonise with NZ and allow up to 20 mg per dosage unit. Several Members argued for consistency with other PPIs. A Member noted, however, that unlike many of the other PPIs there were real questions around the efficacy of this 'half the standard dose' strength for omeprazole. Indeed, 10 mg omeprazole may be sub-therapeutic for the treatment of GORD.

A Member also supported up to 20 mg per dosage unit due to concern with the complicated dosage recommendation that appeared to be required for the 10 mg omeprazole products (two tablets taken daily until symptoms improve and then to reduce to one tablet daily) which may confuse patients and lead to non-compliance. Another Member noted that, given NZ's recent OTC experience with 10 mg omeprazole, it was somewhat reassuring that the MCC felt comfortable with an OTC dose of 20 mg. The Committee generally agreed that the Schedule 3 entry for omeprazole should allow up to 20 mg per dosage unit for the relief of heartburn and GORD, with a pack size limit of no more than 14 days supply.

Members then considered whether there was sufficient grounds for an Appendix H listing for omeprazole. A Member asserted that the various PPIs in Schedule 3 appeared to be sufficient similar that any decision regarding Appendix H should be consistent across the whole class. A number of Members asserted that the concerns raised regarding the request to list pantoprazole in Appendix H (item 12.2.2) would also apply to omeprazole. The Committee generally did not support inclusion of omeprazole in Appendix H.

Several Members additionally queried whether this consideration of omeprazole should extend to the specific isomer esomeprazole. The Committee generally agreed, however, that the current consideration should only focus on omeprazole, noting that it was always open for an interested party to submit a suitable supportive esomeprazole application at some future date.

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The Committee agreed to include omeprazole in Schedule 3 when:

- in preparations containing 20 mg or less per dosage unit of omeprazole for the relief of heartburn and GORD; and
- in a pack containing not more than 14 days of supply.

Schedule 3 – New entry

OMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit of omeprazole 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

OMEPRAZOLE – Amend entry to read:

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

16.1.8 PAZOPANIB

PURPOSE

The Committee considered the scheduling of pazopanib.

BACKGROUND

Pazopanib is an orally administered, multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptors (PDGFR)-α and -β, and stem cell factor receptor (c-KIT). *In vivo,* pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumour xenografts in mice. VEGF and PDGF are growth factors critical to the development and growth of blood vessels. Pazopanib has been used for the treatment of advanced and / or metastatic renal cell carcinoma (US Prescribing Information [PI]).

Pazopanib has not been previously considered by the Committee and it has not been registered in Australia.

Pazopanib is a prescription medicine in New Zealand and unscheduled in Australia.

DISCUSSION - SUBMISSIONS

The November 2009 NZ Medicines Classification Committee (MCC) meeting classified the new chemical entity ‘panzopanib hydrochloride’ as a prescription medicine for the indication for the treatment of advanced and / or metastatic renal cell carcinoma (RCC).

Members noted that the name of this substance was originally misspelt in the MCC minutes as 'panzopanib' and this spelling was also included in the February 2010 pre-meeting *Gazette* notice. NZ MCC has been advised of this erratum.

Members noted that in October 2009, the USFDA granted approval of pazopanib tablets 200 mg and 400 mg for the treatment of patients with advanced RCC. The recommended daily dose is 800 mg.

Members noted that in June 2006, orphan designation was granted by the European Commission for pazopanib for the treatment of RCC, as reported by the EMEA's Public Summary. A Marketing Authorisation Application (MAA) for oral therapy for patients with advanced and/or metastatic RCC was submitted to the EMEA and is currently under regulatory review (http://us.gsk.com/html/media-news/pressreleases/2009/2009_us_pressrelease_10009.htm).

Adverse events (USFDA approved PI)

- The most common AE (more than 20 per cent) reported were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia and vomiting.
- Deaths due to serious adverse events including cerebrovascular accident, gastric cancer, gastrointestinal hemorrhage, hemoptysis, bowel perforation, cardiac failure, myocardial infarction, hepatic failure and pneumonia occurred more commonly in the pazopanib arm in a clinical trial.
- Hepatic dysfunction was included as a boxed warning in the product label and two deaths were associated with hepatic failure.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under Section 52E(1) were (a) the toxicity and safety, (c) the potential hazards and (h) the purposes for which a substance is to be used.

The Committee generally agreed that the condition being treated with pazopanib required medical diagnosis and management; therefore pazopanib was best placed in Schedule 4.

RESOLUTION 2010/58 - 33

The Committee decided to include the new chemical entity pazopanib in Schedule 4.

Schedule 4 – New entry

PAZOPANIB.

16.1.9 PHOSPHODIESTERASE TYPE 5 INHIBITORS

PURPOSE

The Committee considered the scheduling of phosphodiesterase type 5 (PDE-5) inhibitors.

BACKGROUND

There are 6 subtypes of phosphodiesterase inhibitors (PDEs). Sildenafil, tadalafil and vardenafil are inhibitors of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type-5 (PDE-5) in smooth muscle, where PDE-5 is responsible for degradation of cGMP.

At the August 1998 meeting, Members agreed to include sildenafil in Schedule 4. At the February 2003 meeting, the Committee agreed to also include tadalafil in Schedule 4. At the June 2003 meeting the Committee agreed to add vardenafil into Schedule 4. These are the only significant PDE-5 inhibitors that have been specifically considered to date.

At the February 2009 meeting, the Committee discussed the need for a class entry for PDE-5 inhibitors following information that certain medicines purporting to be complementary had been found to contain undeclared synthetic PDE-5 inhibitors. The Committee specifically noted the difference between adulterated goods (containing substances not disclosed) and counterfeit goods (claiming to contain substances that are not present). The Committee agreed to include a class entry for PDE-5 inhibitors in Schedule 4 noting that this entry would capture any adulterated goods containing PDE-5 inhibitors.

At its May 2009 meeting, the New Zealand Medicines Classification Committee (MCC) agreed in principle to a proposal to classify PDE-5 inhibitors as prescription medicines. The MCC noted that the intent was to cover substances with clinically significant PDE-5 inhibitory activity (including the analogues of sildenafil, vardenafil and tadalafil). The MCC requested that appropriate wording for the Schedule entry be identified to ensure that caffeine and other substances with very weak PDE-5 receptor activity were not inadvertently covered.

DISCUSSION - SUBMISSIONS

At its November 2009 meeting, the MCC decided that PDE-5 inhibitors should be included as prescription medicines except:

- when specified elsewhere in the Schedule; or
- when present as an unmodified, naturally occurring substance.

The MCC noted that this wording would ensure that:

- the entry covered all synthetic substances with PDE-5 inhibitory activity unless specified elsewhere in the Schedule;
- the entry covered products containing synthetic PDE-5 inhibitors (i.e. 'natural' healthcare products that have been modified with a synthetic PDE-5 inhibitor); and
- unmodified naturally occurring substances with PDE-5 activity (such as caffeine, pomegranate and extracts of *Epimedium* species) would be exempt. Inclusion of the term "unmodified" would reinforce the concept that the structure of a naturally occurring substance should not be altered.

The MCC also noted that highly concentrated substance would not necessarily be considered as modified and so could be exempt from scheduling.

The MCC specifically noted that the class entry for PDE-5 inhibitors would cover 'nature identical' substances. While 'nature identical' substances may bear the same chemical formula as the naturally occurring substance, they may not possess the same chirality or the same proportion of each optical isomer. This may affect both pharmacological activity and the risk benefit profile of the product.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matter under section 52E (1) included (e) dosage and formulation.

A Member noted that many of the naturally occurring substances with PDE-5 inhibitory activity appear to be foods and may therefore be exempt due to the Appendix A general exemption for food. The Member noted that in this circumstance, NZ and Australian entries for PDE-5 inhibitors would already be essentially harmonised. Another Member noted, however, that natural extracts for use in healthcare products would probably not qualify for this general exemption.

Members agreed that it would be beneficial to clarify the PDE-5 inhibitors entry to exempt such substances where they occur naturally (i.e. caffeine, pomegranate juice). A Member also noted that in addition to naturally occurring substances, such as plant extracts, the MCC had also stated that this should be interpreted as including nature identical preparations that may not necessarily originate from a natural source. Members agreed to minute that the SUSDP exemption should also be interpreted as including nature identical substances.

Members noted that, if concerns did arise from a particular naturally occurring PDE-5 inhibitor, this class entry exemption would in no way preclude the Committee from considering individual scheduling for the specific substance.

RESOLUTION 2010/58 - 34

The Committee decides to harmonise with New Zealand and amend the class entry for phosphodiesterase type 5 inhibitors to exempt unmodified, naturally occurring instances of the substance.

Schedule 4 - Amendment

PHOSPHODIESTERASE TYPE 5 INHIBITORS – Amend entry to read:

PHOSPHODIESTERASE TYPE 5 INHIBITORS **except**:

(a) when separately specified in these Schedules; or

(b) when present as an unmodified, naturally occurring substance.

16.2.1 MEDICINES HARMONISED

PURPOSE

The Committee noted medicines recently harmonised through decisions by the New Zealand Medicines Classification Committee (MCC).

BACKGROUND

At its November 2009 meeting, the MCC decided to harmonise with recent NDPSC scheduling decisions by classifying a number of new medicines and making one amendment to current New Zealand classifications.

DISCUSSION - SUBMISSIONS

Members noted that at the November 2009 MCC meeting the following substances were harmonised with the current SUSDP scheduling:

- **Human papillomavirus vaccine** and **Japanese encephalitis vaccine** – Prescription medicine. *(Reflecting the June 2009 NDPSC decision).*

Members also noted that one substance was essentially harmonised:

- **Loperamide** – NZ amended the prescription medicine entry so that the condition states "except when specified elsewhere in this Schedule". (*Essentially harmonised* – Reflecting the June 2009 NDPSC decision to amend the Schedule 2 entry for loperamide to further clarify that liquid preparations are Schedule 4. The MCC decision ensured that liquid entries would be covered by the prescription medicine classification.)

RESOLUTION 2010/58 - 35

The Committee noted that the scheduling of human papillomavirus vaccine, Japanese encephalitis vaccine and loperamide is now harmonised following decisions at the November 2009 MCC.

16.3.1 MEDICINES NOT HARMONISED

PURPOSE

The Committee noted medicines not harmonised through decisions by the New Zealand Medicines Classification Committee (MCC) at its November 2009 meeting.

BACKGROUND

At the June 2009 NDPSC meeting, the Committee decided to include a class entry for HMG-CoA reductase inhibitors ('statins') in Schedule 4. The wording for this entry was further amended at the October 2009 meeting.

Also at the October 2009 meeting, the Committee decided to include an entry for red yeast rice in Schedule 4.

At its November 2009 meeting, the Medicines Classification Committee (MCC) decided not to harmonise with the June 2009 NDPSC decision to include the class entry for statins. Due to differences in timetables, the MCC had not yet considered the October 2009 NDPSC decision relating to the amendment to the class entry for statins and inclusion of a new entry for red yeast rice.

DISCUSSION - SUBMISSIONS

The MCC delayed the decision to include the proposed class entry for HMG-CoA reductase inhibitors ('statins') in prescription medicines, stating the following main issues:

- In New Zealand classifications it is necessary to differentiate dietary supplements from medicines, as a general class entry would also cover foodstuffs and dietary supplements. Hence, the class entry for statins would also inadvertently cover red yeast rice extract, which contains lovastatin.
- Further information was required on the indications and side effects of red yeast rice extract containing lovastatin before a decision to harmonise with Australia on statins could be made.

RESOLUTION 2010/58 - 36

The Committee noted that the New Zealand and Australian scheduling entries for HMG-CoA reductase inhibitors ('statins') would not be harmonised following the MCC's decision at its November 2009 meeting.

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC)

No items.

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

No items.

19. INFORMATION ITEMS (PHARMACEUTICALS)

19.1 XXXXX

20. GAZETTAL NOTICES

The Committee noted the post-October 2009 meeting Gazette Notice dated 23 December 2009.

The Committee noted the pre-February 2010 meeting Gazette Notice dated 2 December 2009.

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES AND ERRATA

21.1.1 EDITORIAL AMENDMENTS - AMBRISENTAN

PURPOSE

The Committee considered editorially amending the Schedule 4 ambrisentan entry.

BACKGROUND

Members noted that the current Schedule 4 entry for ambrisentan in SUSDP 24 Amendment 1 was:

AMBRISENTAN.

Members also noted that in February 2010, the Drafting Advisory Panel advised that as ambrisentan is also included in Appendix D, the Schedule 4 entry required a '#' symbol.

RESOLUTION 2010/58 - 37

The Committee decided to editorially amend the Schedule 4 entry for ambrisentan by adding a '#'.

Schedule 4 – Amendment

AMBRISENTAN – Amend entry to read:

AMBRISENTAN.

21.1.2 EDITORIAL AMENDMENTS – PANTOPRAZOLE AND RABEPRAZOLE

PURPOSE

The Committee considered editorially amending the existing Schedule 3 entries for pantoprazole and rabeprazole.

BACKGROUND

While considering new Schedule 3 entries for lansoprazole (item 16.1.6) and omeprazole (item 16.1.7) Members noted that these should be consistent with the existing Schedule 3 entries for pantoprazole and rabeprazole, i.e. in oral preparations containing x mg or less of x for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply.

However, Members agreed that for clarity and consistency, this wording should be editorially amended to include 'per dosage unit'.

The Committee incorporated this change into the new Schedule 3 entries for lansoprazole and omeprazole (under items 16.1.6 and 16.1.7 respectively).

RESOLUTION 2010/58 - 38

The Committee decided to editorially amend the Schedule 3 entries for pantoprazole and rabeprazole to include 'per dosage unit'.

Schedule 3 – Amendments

PANTOPRAZOLE – Amend entry to read:

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

RABEPRAZOLE – Amend entry to read:

RABEPRAZOLE in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply

21.2 SUSDP 24 AMENDMENT 3 - EDITORIALS

PURPOSE

The Committee considered possible editorials to the draft SUSDP 24 Amendment 3 (SUSDP 24/3).

BACKGROUND

Members noted that a review of the draft SUSDP 24/3 by the Drafting Advisory Panel resulted in one proposed editorial change to improve clarity and consistency with other entries.

Members noted the recommendation that the word 'and' after sub (b)(ii) of the Schedule 3 amendment for codeine be removed as it is superfluous, not consistent with other entries and may cause confusion as a result.

RESOLUTION 2010/58 - 39

The Committee decided to editorially amend the Schedule 3 entry for codeine by removing a superfluous 'and'.

Schedule 3 - Amendment

CODEINE – Amend entry to read:

CODEINE when:

(a) not combined with any other opiate substance;

(b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:

(i) in divided preparations containing 12 mg or less of codeine per dosage unit; or

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

(c) labelled with a recommended daily dose not exceeding 100 mg of codeine; and

(d) in packs containing not more than 5 days of supply at the maximum dose recommended on the label,

except when included in Schedule 2.

22. CLOSURE AND NEXT MEETING

The Chair closed the Meeting at 11:30am, 17 February 2010 and advised that the next Meeting of the NDPSC will be held on 22 – 23 June 2010.