Australian Government

Department of Health and Ageing

FINAL DECISIONS & REASONS FOR DECISIONS BY DELEGATES OF THE SECRETARY TO THE DEPARTMENT OF HEALTH AND AGEING

JUNE 2011

Delegates' final decisions on scheduling matters:

- Initially referred to the February 2011 meeting of the Advisory Committee on Chemicals Scheduling (ACCS) [**ACCS#1**];
- Initially referred to the February 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS) [**ACMS#2**];
- Initially referred to the February 2011 joint meeting of the ACCS and the ACMS [**ACCS-ACMS#2**]; or
- Considered as delegate-only matters i.e. were not referred to an advisory committee.

Notice under subsections 42ZXZS and 42ZCZX of the Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary to the Department of Health and Ageing hereby gives notice of delegates' final decisions for amending the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* – SUSMP) under subsections 42ZCZS and 42ZCZX of the Regulations. This notice also provides the reasons for each decision and the date of effect of the decision. Edited versions of further submissions on interim decisions for matters referred to ACCS#1, ACMS#2 or ACCS-ACMS#2 are also available at www.tga.gov.au/industry/scheduling-submissions.htm.

Matters referred to ACCS#1, ACMS#2 and ACCS-ACMS#2

Delegate's interim decisions on recommendations by ACCS#1, ACMS#2 and ACCS-ACMS#2 were published on 27 April 2011, accessible at www.tga.gov.au/industry/scheduling-decisions-interim.htm. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions (published 15 December 2010, together with a supplementary invitation published 16 December 2010 – both accessible at www.tga.gov.au/newsroom/consult-scheduling-acmcs.htm).

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, that delegate may make a final decision confirming, varying or setting aside the interim decision only after considering any further valid submissions. If no further submissions were received then the delegate may choose to confirm the interim decision as the final decision.

Further submissions from parties other than those who made a valid submission in response to the original invitation or the applicant, or those received after the closing date, need not be considered by the delegate.

Matters not referred to an advisory committee

A delegate may decide not to refer a matter to an advisory committee and instead may make a final decision on matters. Guidance for the delegate when deciding not to refer a matter to an advisory committee is set out in the Scheduling Policy Framework (SPF) accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Implementation

The amendments arising from this notice will be incorporated into the SUSMP through an amendment which will be available for purchase from National Mailing and Marketing Pty Ltd, telephone (02) 6269 1035. The SUSMP and its amendments are also available electronically at the ComLaw website, a link to which can be found at http://www.tga.gov.au/industry/scheduling-poisons-standard.htm.

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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	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [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

CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments
CRC	Child-Resistant Closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
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
GP	General Practitioner
HCN	Health Communication Network
HCP	Health Care Provider
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	Medicines Evaluation Committee (now Advisory Committee on Non-Prescription Medicines [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
NOAEC	No Observed Adverse Effect Concentration
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
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (was Office of Prescription and Non-prescription Medicines)
OOS	Out of Session

OTC	Over-the-Counter
PACIA	Plastics And Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
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
WHO	World Health Organization
WP	Working Party
WS	Warning statement

PART A – FINAL DECISIONS ON MATTERS REFERRED TO AN ADVISORY COMMITTEE

1. MATTERS INITIALLY REFERRED TO ACCS#1 – FEBRUARY 2011

1.1 CEFQUINOME

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of cefquinome and decided to seek advice from the ACCS on the following:

Cefquinome – proposal to include cefquinome in Schedule 4.

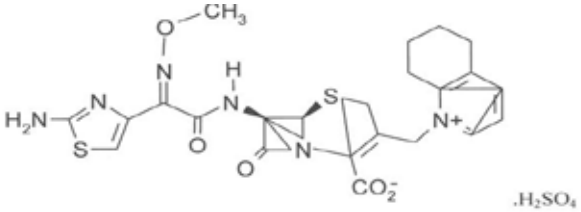
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 4 entry be created for cefquinome. The Committee also recommended an implementation date of no more than 6 months after the delegate's final decision.

BACKGROUND

Currently the SUSMP prefers the use of sulfate rather than sulphate.

Cefquinome sulfate belongs to the cephalosporin group of antibiotics which act by inhibition of cell wall synthesis, resulting in bacterial cell death. The structure is:



XXXXX has submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking the approval of a new active ingredient, cefquinome sulfate, and the registration of XXXXX.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for cefquinome sulfate. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Cefquinome is not specifically scheduled. It would, however, be captured by the Schedule 4 group entry for antibiotic substances.

INITIAL SUBMISSIONS

Applicant's Submission

The XXXXX Risk Assessment Technical Report concluded that, based on the toxicity profile of cefquinome sulfate and the need for veterinary diagnosis of the indicated condition XXXXX, cefquinome sulfate should be included in Schedule 4.

Other XXXXX conclusions included:

- There were no objections on human health grounds to the approval of the active ingredient cefquinome sulfate or to the registration of the product.
- As the product was an antibiotic and not intended to be used in food-producing animals, establishment of an ADI and ARfD for cefquinome sulfate was not required. If cefquinome sulfate were to be used in the future to treat food producing animals, a microbial ADI and/or toxicological ADI would have to be established.
- XXXXX.
- No re-entry, re-handling, warning or precautionary statements were required.

Members noted that the applicant submitted studies to the APVMA on toxicokinetics and metabolism, acute toxicity, subchronic toxicity, genotoxicity, developmental and reproductive toxicity. Although most studies did not strictly conform to current test guidelines or standards of reporting, they were considered acceptable by the evaluator for the assessment of the toxicology profile of cefquinome sulfate in this case.

Toxicology

Members noted the following toxicology summary for cefquinome sulfate:

XXXXX

- Cefquinome sulfate had low acute oral toxicity XXXXX, low acute intravenous XXXXX and subcutaneous toxicity XXXXX.
- Cefquinome sulfate was not a skin sensitiser in XXXXX. No acute inhalation toxicity, skin or eye irritation studies were provided. However, based on the use pattern of the product, exposure by these routes was likely to be minimal.
- Repeat-dose oral toxicity studies were performed in XXXXX. The main toxicological effect noted in XXXXX was increased kidney weight and changes in clinical chemistry and urinalysis parameters suggestive of an alteration in renal function, as well as vacuolisation of the epithelial cells of the convoluted proximal tubules of the kidney. Enlargement of the caecum was also seen but without corroborative histological findings. This was likely due to changes in the intestinal microflora, which is a side effect common to cephalosporin antibiotics. In XXXXX, interference with hepatic synthesis of certain molecules such as cholesterol and

triglycerides was observed, and liver weights were increased without corroborative histological findings.

- In a XXXXX reproduction study, there were no effects on reproductive parameters, and cefquinome sulfate was not a developmental toxicant XXXXX developmental toxicity study. Studies on carcinogenicity were not provided, however, cefquinome sulfate was not mutagenic or genotoxic in *in vitro* studies, or genotoxic in an *in vivo* study.

Members additionally noted the results of a study designed to determine the minimum inhibitory concentration of cefquinome sulfate against a range of bacteria genera and strains that were representative of the human colonic microflora, bacterial suspensions were inoculated into agar plates at two different densities. No strain was sensitive to cefquinome at concentrations below XXXXX. The most sensitive species was XXXXX.

Members noted that no toxicity studies were submitted for the product. The acute oral and dermal toxicity was estimated from the available toxicity data on the active constituent and other constituents as summarised below:

Toxicity end point	Toxicity of Product
Oral	Low
Dermal	Low
Inhalational	No data
Skin irritation	No data
Eye irritation	No data
Skin sensitisation	Unlikely

Use Pattern / Exposure

Members noted the following summary of use pattern and exposure information from the XXXXX report:

- XXXXX.
- The product would be administered by qualified veterinarians and trained farmers, so any potential for exposure will be restricted to these trained individuals who would be aware of the possible toxicity associated with the product.
- XXXXX.

Hazard Classification

Cefquinome is not listed on Safe Work Australia's Hazardous Substances Information System (HSIS) Database. The XXXXX has determined that both cefquinome sulfate and the product are not classified as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances.

Applicant's Response to the Evaluation Report

XXXXX had considered the XXXXX Report, including the scheduling recommendation, and advised that there were no comments.

February 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that relevant matters under Section 52E (1) included (a) risks and benefits; and (b) the purpose and extent of use.

Members noted that as cefquinome sulfate was an antibiotic substance it was already captured by Schedule 4. Members also agreed that there was no information to suggest that anything other than supply by prescription should apply to the availability of cefquinome sulfate. For clarity, Members agreed that a separate specific listing in Schedule 4 would be appropriate.

Members then discussed the wording of a specific Schedule 4 entry. Members noted the precedent for scheduling a parent substance rather than a specific salt unless the salt has unique toxicity. Members agreed that there were no data to indicate unique toxicity and a parent entry for cefquinome was considered to be sufficient. A Member also suggested limiting the specific entry to animal use only, on the presumption that the group entry for antibiotic substances would still capture any potential human use. Other Members clarified that the group entry would not apply if there was a specific entry i.e. limiting the cefquinome entry to animal use would mean that cefquinome for any other use, including human use, would then be unscheduled. A Member particularly raised the concern that inappropriate access through importation for personal human use could occur if such use were not classed as Schedule 4. The Committee agreed that the specific entry needed to remain broad to capture all potential uses of cefquinome.

A Member noted that there had been considerable controversy overseas, particularly in the US, over the use of cefquinome in animals. Cefquinome is a 4th generation cephalosporin and the Member had concerns about the use of a 4th generation antibiotic in animals as this could potentially lead to increases in antibiotic resistance. Members noted advice that the APVMA would investigate these claims, noting that the cost of this antibiotic was likely to mitigate any propensity for misuse or abuse. Members noted that while this was an issue that APVMA was aware of, it was yet another reason for cefquinome to be Schedule 4.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACCS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits and (b) the purpose and extent of use.

DELEGATE'S INTERIM DECISION

The delegate decided to include cefquinome in Schedule 4. The delegate decided that an implementation date of 1 January 2012 was appropriate (i.e. six months after publication of the final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that cefquinome be included in Schedule 4. The delegate also confirmed an implementation date of 1 January 2012.

Schedule 4 – New entry

CEFQUINOME.

1.2 DERQUANTEL

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of derquantel and decided to seek advice from the ACCS on the following:

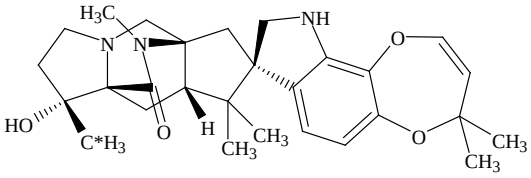
Derquantel – proposal to include derquantel in Schedule 6 with a cut-off to Schedule 5 for preparations containing 1 per cent or less of derquantel.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 6 entry be created for derquantel, with a cut-off to Schedule 5 for preparations containing 1 per cent or less of derquantel. The Committee also recommended an implementation date of no more than six months after the delegate's final decision.

BACKGROUND

Derquantel is a member of the spiroindole class of anthelmintics. It acts as a selective nicotinic antagonist in somatic muscle by competing for the ganglionic nicotinic cholinergic receptors, thus inducing flaccid paralysis in parasitic nematodes. Its structure is:



XXXXX.

XXXXX has submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking approval for the active ingredient derquantel and the registration of XXXXX.

The XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for derquantel. The delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Derquantel is not currently scheduled.

INITIAL SUBMISSIONS

Applicant's Submission

The XXXXX Report found that derquantel presents a hazard for repeated use, and although it is considered unlikely to produce irreversible toxicity it is a competitive nicotinic antagonist that has produced clinical signs of neurotoxicity in XXXXX. Thus, the evaluator concluded that derquantel met the requirements of a Schedule 6 chemical. The evaluator recommended that derquantel be included in Schedule 6 with a 1 per cent cut-off to Schedule 5.

Other XXXXX conclusions included:

- There were no objections on human health grounds to the approval of active ingredient derquantel XXXXX.
- The ADI for derquantel was established at 0.0005 mg/kg bw/d based on a LOEL of 0.1 mg/kg bw/d in a XXXXX and using a 200-fold safety factor.
- The ARfD for derquantel was established at 0.01 mg/kg bw based on a NOEL of 1 mg/kg bw in an XXXXX and using a 100-fold safety factor.
- Recommended labelling included the safety directions "*May irritate the skin*" and "*Avoid contact with the skin*". Members noted, however, that Appendices E and F do not apply to products regulated by the APVMA. APVMA sets these labelling requirements as part of its product approval process.
- No re-entry, re-handling, warning or precautionary statements are required.

Members also noted the following further information regarding derquantel's mode of action in mammals:

- The proposed mode of action for derquantel is that of a competitive nicotinic antagonist.
- When the neurotransmitter acetylcholine is released across the ganglionic synapse, it interacts and activates the nicotinic cholinergic receptor. This leads to ganglionic nerve transmission and stimulation of the sympathetic and parasympathetic nervous systems. The agonist, nicotine, can also interact and activate the nicotinic cholinergic receptor. Nicotine induced physiological effects include an increase in blood pressure and it also promotes secretion of saliva and sweat.
- Ganglionic antagonists competitively interact with the nicotinic cholinergic receptor and, thus, block nerve transmission and stimulation of the sympathetic and parasympathetic systems. Blockade of sympathetic tone to arterioles by a ganglionic antagonist results in vasodilation, increased peripheral blood flow, reduced total peripheral resistance and a fall in arterial blood pressure.

Toxicology – Technical Grade Active

Members noted the following toxicology summary for derquantel:

XXXXX

- Derquantel has low acute oral XXXXX, dermal XXXXX and inhalational toxicity XXXXX (Members noted that the acute oral and inhalation toxicity endpoints, although termed as "low toxicity" by the evaluator, actually aligned with the Scheduling Policy Framework factors for Schedule 6). Derquantel is a slight eye but not a skin irritant in XXXXX. It is not a skin sensitiser in XXXXX.
- Derquantel is a competitive nicotinic antagonist, which blocks nicotinic ganglionic stimulation of cells expressing muscle-type by competing for the ganglionic nicotinic cholinergic receptors. In repeat dose studies in XXXXX, clinical signs consistent with this mode of action XXXXX were seen at all dose levels in a dose-dependent manner, including the lowest dose of XXXXX. XXXXX. There was evidence to suggest that the dose of XXXXX was approaching a threshold (NOEL). In a XXXXX study in XXXXX, neurological assessment revealed adverse neurological signs at XXXXX.
- No dedicated neurotoxic study was submitted, however, a battery of functional observations was undertaken as part of several repeat dose studies. Although no significant treatment related effects were seen on Functional Observational Battery (FOB) and motor activity parameters, clinical signs of neurotoxicity were clearly seen in XXXXX, as described above.
- The primary target organ of derquantel in XXXXX was the liver. Derquantel is not a reproductive or developmental toxicant, and it is not an *in vivo* genotoxicant.

- No carcinogenicity studies were submitted. However, this is considered acceptable in this instance as:
  - derquantel is not considered to be an *in vivo* genotoxicant;
  - derquantel is a member of the chemical class spiroindole that are not known to be animal or human carcinogens;
  - there is a lack of significant preneoplastic findings in the XXXXX study; and
  - systemic toxicity studies do not indicate that derquantel may be associated with effects known to be linked with epigenetic mechanisms of carcinogenicity that are relevant to humans.
- XXXXX.

Toxicology – Product XXXXX

Members noted the following toxicology summary for the product:

XXXXX

- The low oral LD_{50} was estimated to be XXXXX. The low dermal LD_{50} in XXXXX was greater than XXXXX. The inhalational toxicity was also low in XXXXX, with a 4-h LC_{50} greater than XXXXX. The product was a slight skin irritant in XXXXX, but was not an eye irritant in XXXXX. The XXXXX was negative for skin sensitisation.
- XXXXX. As reversible signs of clinical neurotoxicity have only been seen at a relatively high dose, and noting the use pattern for the product, the evaluator considered that Schedule 5 was appropriate for 1 per cent or less derquantel based on slight skin irritation.
- XXXXX.

Use Pattern / Exposure

- XXXXX.
- The product is not intended for home use and exposure to members of the public is not expected to occur. The public, however, may be exposed to XXXXX.
- XXXXX. The main route of exposure to the product will be dermal, though ocular exposure may also occur. Inhalational exposure is considered unlikely.
- No worker exposure studies were provided. In the absence of these studies or models, the occupational health and safety assessment was performed by calculating the tolerable daily doses of derquantel XXXXX and then considering whether worker's exposure would approach or exceed the tolerable daily dose.
- The tolerable daily dose for derquantel would be 7 mg/d (LOEL of 0.1 mg/kg bw/d x 70 kg). Assuming 100 per cent dermal absorption, a worker would only need to be exposed to XXXXX of the product in order to absorb 7 mg of derquantel. Using a

Margin Of Exposure (MOE) of 200, the tolerable daily dose would be contained in XXXXX of the product. Therefore, it is considered highly likely that a worker would be exposed to this amount of the product during a normal working day, particularly in the event of a spill. Appropriate Personal Protective Equipment (PPE) has been recommended for acute risks to protect workers from skin irritation and systemic toxicity when using the product.

- XXXXX, no post application exposure was expected.

Hazard Classification

- Derquantel is not listed as a hazardous substance on the on Safe Work Australia's HSIS Database. Derquantel has a neurotoxic potential, and has produced clinical signs of toxicity in both XXXXX in repeated dose oral studies. In a XXXXX study in XXXXX, adverse neurological signs XXXXX were observed in animals at XXXXX, with effects seen in XXXXX at lower concentrations.
- The evaluator therefore recommended classification of derquantel as a hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004), with the risk phrase (R48/22): *Danger of serious damage to health by prolonged oral exposure*.
- XXXXX.

Applicant's Response to the Evaluation Report

XXXXX has considered the XXXXX Report, including the scheduling recommendation, and accepted the XXXXX proposal for scheduling.

February 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that relevant matters under Section 52E (1) included (a) risks and benefits; (b) the purpose and extent of use; and (c) toxicity.

Members discussed whether derquantel should be captured in Schedule 6. A Member noted that the neurotoxicity effects were minor and mostly transient, with most concerns coming from longer term studies. It was also noted that the acute oral and inhalation toxicity endpoints were consistent with a Schedule 6 parent entry. A Member was concerned that the acute endpoints may not have reflected effects in the most sensitive species, noting that in one XXXXX study an exposure of XXXXX caused deaths. Another Member noted, however, that a big difference between species was not unusual, and that XXXXX can be very sensitive to some substances. Members agreed that a Schedule 6 parent entry for derquantel was appropriate.

Members considered if there should be a low concentration cut-off from the Schedule 6 parent entry, noting the evaluator's proposal for a Schedule 5 cut-off for preparations containing 1 per cent or less derquantel. A Member noted that there was repeat dose data for the product which supported a Schedule 5 listing. The Member also reiterated that the neurotoxicity effects were only seen at high levels and asserted that this was also supportive of allowing a low level cut-off. A Member was concerned, however, that due to the high dermal absorption small exposures could exceed the daily tolerable dose, especially for a child. A Member noted that occasionally exceeding the daily tolerable dose was not a large concern, as this dose was based on lifetime exposure. Members generally agreed that accidental exposure, such as to a child on a farm, was unlikely to be an ongoing frequent exposure.

A Member also noted that the limited use pattern of derquantel meant little or no risk of domestic use, and dermal exposure through occupational use would be mitigated by the prescribed personal protective equipment (PPE). A Member remained concerned, however, about relying on compliance with PPE and felt that perhaps a POISONS signal heading (i.e. Schedule 6) would increase occupational users' PPE compliance.

A Member noted that although derquantel had a high dermal absorption, it did not accumulate and was readily excreted. The Member also noted that the effects of concern that were the basis for the tolerable daily dose and acute reference dose were mild endpoints, such as transient ocular effects, rather than acute toxicity or other serious endpoints. The Member also recalled that the acute toxicity of derquantel, at concentrations of 1 per cent or less, was very low, noting that this was based on submitted data.

Several Members therefore argued that, at worst (and very rarely), a child would be exposed to a 1 per cent preparation resulting in some transient effects which were reversible. These Members asserted that labelling the product as POISON seemed disproportionate to this risk. A Member also noted that 1 per cent derquantel appeared comparable with the risks associated with other current listings in Schedule 5. A majority of Members agreed that a cut-off to Schedule 5 for preparations containing 1 per cent or less of derquantel was appropriate.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendation of the ACCS regarding a parent entry for derquantel in Schedule 6 was clear and appropriately supported by the toxicity profile for derquantel. The delegate agreed with this recommendation.

The delegate was less convinced regarding support for the ACCS recommendation to allow a cut-off to Schedule 5 for preparations containing 1 per cent or less of derquantel, noting that the ACCS Members were not unanimous in supporting this recommendation.

A key issue for the delegate was the marked species-differences in susceptibility to the nicotinic antagonistic effects of derquantel between XXXXX. In XXXXX, lethal doses

and those producing clinical symptoms were higher than in XXXXX. In the absence of an LD_{50} estimates in XXXXX, XXXXX LD_{50} estimates XXXXX were relied on by the Committee in considering the proposed cut-off for preparations containing 1 per cent or less of derquantel. However, single dose and repeated-dose studies in XXXXX were used to derive both the ADI and the ARfD, using the onset of clinical signs (admittedly mild and transient) as the signal toxic effect.

In the case of the ARfD, a conventional 100x safety factor was applied to the NOAEL of 1 mg/kg (LOAEL 5 mg/kg), while a 200x safety factor was applied to the LOAEL (0.1 mg/kg/d in XXXXX) to derive the ADI. Applying a linear extrapolation to the acute toxicity NOAEL and LOAEL in XXXXX, a 1 per cent derquantel preparation would be expected to show signs of toxicity between 100-500 mg/kg. The delegate did note, however, that while this dose range was consistent with the Scheduling Policy Framework LD_{50} factors for Schedule 6 (50-2000 mg/kg), there were likely to be significant differences between doses producing transient effects due to nicotinic receptor antagonism, and those causing death.

The delegate noted that these species-differences were likely to be due to differences in receptor sensitivity, rather than differences in metabolism or toxicokinetics. The delegate noted that an ACCS Member had commented on the fact that XXXXX also appeared to be highly sensitive to derquantel lethality. The ACCS advised that such a species variation in sensitivity was not considered to be unusual, but that it would not necessarily be relevant in assessing human susceptibility for scheduling purposes.

The delegate also noted that a Member queried whether the required signal wording under the proposed Schedule 5 exemption (CAUTION) would adequately prompt additional caution on the part of a product's user, given that daily dermal exposure to as little as 0.7 mL of a 1 per cent preparation would provide exposure equivalent to the XXXXX LOAEL in XXXXX (0.1 mg/kg/d), assuming dermal bioavailability of 100 per cent.

The delegate concluded that, taking the above matters into consideration, the case for a cut-off from Schedule 6 for preparations containing 1 per cent or less of derquantel had not been established.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) the purpose and extent of use; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate decided to create a Schedule 6 entry for derquantel, with no cut-offs. The delegate decided that an implementation date of 1 January 2012 was appropriate (i.e. six months after publication of the delegate's final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate decided to create a Schedule 6 entry for derquantel, with no cut-offs. The delegate also decided on an implementation date of 1 January 2012.

Schedule 6 – New entry

DERQUANTEL.

1.3 DIETHYLHEXYL PHTHALATE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of diethylhexyl phthalate and decided to seek advice from the ACCS on the following:

Diethylhexyl phthalate (DEHP) – proposal to schedule DEHP, including consideration of:

- a parent entry in Schedule 6 or 7;
- prohibition of cosmetic use through listing in Appendix C.

The delegate also decided to seek advice on potential cut-offs and exemptions, including possibly restricting the use in toys and childcare articles to less than 0.05 per cent.

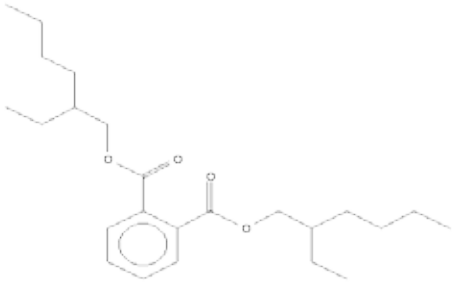
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the use of DEHP in cosmetic products be prohibited by inclusion in Appendix C. The Committee also recommended an implementation period of six months after the delegate's final decision.

The Committee additionally recommended that the delegate advise TGA of the need to review concerns from the potential leaching of DEHP when used in some medical devices.

BACKGROUND

DEHP is a benzenedicarboxylic acid ester of phthalic acid (a chemical class commonly referred to as phthalates). The CAS and IUPAC name for DEHP is bis(2-ethylhexyl) phthalate and the chemical structure is:



DEHP is one of the most extensively used phthalates worldwide. In the USA, approximately 97 per cent of DEHP is used as a plasticiser in polyvinyl chloride (PVC). In the European Union (EU), DEHP use represents around half of the total volume of phthalates used as plasticisers.

In Australia DEHP, and DEHP containing PVC, is used in flooring, waterproofing materials, cable sheathing/insulation, PVC labels, surface repair resin moulds, epoxy and polyurethane products, rubber components in automotive brake assemblies and hot melt adhesives for automotive assembly and repair. DEHP is also used in fragrance bases for perfumery and cosmetic products. DEHP is additionally used as a plasticiser in medical devices such as blood bags and dialysis equipment.

DEHP was declared a Priority Existing Chemical (PEC) for public health risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1998* in March 2006. The decision for declaration was based on:

- ubiquitous use of phthalates, including DEHP, as plasticizers in industrial and consumer products;
- consumer products being significant sources of repeated and long term exposure of the public via migration and leaching;
- the potential for adverse health effects, particularly reproductive effects, from DEHP exposure; and
- current restrictions overseas for the use of DEHP in certain consumer products.

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) PEC Review on DEHP included a scheduling recommendation. This review was therefore referred by NICNAS to the delegate for consideration. The delegate agreed that this was a matter for scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Not currently scheduled. Dimethylphthalate in sunscreens or personal insect repellents for human use (except in preparations containing 0.5 per cent or less of

dimethylphthalate) is currently listed in Appendix C, but appears sufficiently different in structure from DEHP as to not capture DEHP as a derivative.

INITIAL SUBMISSIONS

Applicant's Submission – NICNAS's Priority Existing Chemical Assessment Report

The NICNAS PEC report found that, based on the toxicity profile of DEHP, it would be appropriate to prohibit cosmetics containing this substance, and requested that DEHP be listed in Appendix C to limit the potential exposure of the public to DEHP from use in cosmetics. This recommendation was based on:

- The estimate of the margin of exposure (MOE) for use of DEHP in cosmetics indicated that the risk of reproductive toxicity for the general population was unacceptable. Reproductive toxicity was a serious long term health effect.
- At this time there were no restrictions in Australia on the use of DEHP in cosmetics and there was a potential for the introduction and widespread use of cosmetic products containing DEHP.
- The PEC report indicated that use of DEHP in cosmetic products (in the EU) and personal care products (in California) had been prohibited. In September 2009, Canada added DEHP to its List of Prohibited and Restricted Cosmetic Ingredients.
- The PEC report further indicated that there were no regulatory restrictions on the use of DEPH in cosmetics in Asia and other non-EU countries. This raised the possibility of importing DEHP containing cosmetics manufactured in these countries.

The PEC report also recommended that the Australian Competition and Consumer Commission (ACCC) consider appropriate regulatory measures to limit exposure to DEHP resulting from the use of DEHP in toys and childcare articles where significant mouth contact may occur. This recommendation was based on the following findings of the PEC assessment:

- Worst case estimates of the MOE for use of DEHP in children's toys and childcare articles indicated that the risk of reproductive toxicity in children from the use of these products containing DEHP was unacceptable.
- Oral exposure to DEHP through mouthing of toys and childcare articles was the major route of exposure to DEHP. Reproductive developmental toxicity in children was a serious long term health effect.
- There were no restrictions in Australia on the use of DEHP in consumer products including children's toys and childcare articles and there was a potential for introduction and subsequent exposure of children to DEHP via these products.
- The NICNAS's referral letter to the delegate indicated that the ACCC had already declared certain products containing DEHP unsafe under the *Trade Practices Act 1974* (in January 2011 this Act was renamed as the *Competition and Consumer Act 2010*). Members noted that in March 2010, the ACCC enforced an interim ban

(effective until 2 September 2011) restricting the supply of certain children's plastic products, including toys, childcare articles, and eating vessels and utensils that contain, or have a component that contains, more than 1 per cent by weight DEHP. The ban applied to those products that could readily be sucked and/or chewed and were intended to be use by children up to and including 36 months of age.

- DEHP was not included in the Australian/New Zealand Standard AS/NS ISO 8124 *Safety of Toys* and prior to the ACCC action there were no restrictions on the use of DEHP in consumer products, including toys.
- The EU and the USA have restricted the use of DEHP to less than 0.1 per cent (by weight) of the plastic used in any type of toys and childcare articles and Canada was in the process of implementing a similar restriction.

Toxicology

Members noted the following toxicology summary for DEHP from the PEC Report:

Absorption, distribution, metabolism and excretion.	
Rate and extent of oral absorption.	Completely and rapidly absorbed from the gastrointestinal tract. Most of the administered DEHP was systematically absorbed and excreted in urine. Bioavailability in both children and adults was estimated to be 100%.
Dermal absorption.	*In vivo* experiments conducted on rats and guinea pigs show that 9% and 26% of the applied DEPH was absorbed respectively. Human skin was less permeable (4-fold) to DEHP than rat skin therefore the bioavailability of DEHP in humans was not likely to be exceed 5%.
Distribution.	Liver, kidney, testes and blood were the main distribution sites. The injected DEHP rapidly distributed but there was no evidence of accumulation.
Metabolism.	DEHP is rapidly hydrolysed by lipases to monoethylhexyl phthalate and 2-ethylhexanol. Lipases are found in all tissues, especially in the pancreas, therefore rapidly metabolise in the intestine.
Elimination and excretion.	Orally administered DEHP was excreted mainly as metabolites with small amount of the parent compound. In rats and mice elimination was rapid with 85-95% excreted in the first 24 hours and in humans 75% was excreted within 2 days.

Acute toxicity		
Study	**Species**	**Result**
Oral	Rat	LD_{50} > 20000 to > 40000 mg/kg bw.
Oral	Mouse	LD_{50} > 9860 mg/kg bw
Dermal	Rabbit	LD_{50} = 24750 mg/kg bw
Inhalational (4 hours)	Rat	LC_{50} > 10.62 mg/L
Intravenous	Rat	LD_{50} =200 mg/kg bw
Skin and eye irritation	Rabbit	Minimal irritant
Skin sensitisation	Guinea pig	Non-sensitiser.

Genotoxicity	Non-genotoxic

Carcinogenicity	Increased incidences of hepatocellular adenomas and carcinomas were observed in mice. The LOAEL for tumour induction in male mice was 292 mg/kg bw/d. The NOAEL was 98 mg/kg bw/d.
Reproductive toxicity	Higher doses resulted in decreased male reproductive organs, including

	testes and prostate, weights, decreased sperm motility, sperm concentrations and complete infertility. A NOAEL for effects on fertility in mice was 14 mg/kg bw/d and LOAEL was 140 mg/kg bw/d.

Developmental toxicity	DEHP induced overt structural malformations (mainly tail, brain, urinary tract, gonads vertebral column and sternum) in rats. More subtle effects, such as anogenital distance (AGD) was also recorded in several other studies. Based on reduced AGD, a LOAEL of 113 mg/kg bw/d was determined in rats.

Neurotoxicity and delayed neurotoxicity	Not determined.

- In animals, DEHP exhibited low acute oral, dermal and inhalation toxicity. Intravenous and intraperitoneal administration of DEHP resulted in higher acute toxicity than oral or dermal administration; however, the acute toxicity via these routes was still low. Members also noted that such exposures were very limited. Therefore, DEHP was expected to have low acute toxicity in humans.
- DEHP induced minimal skin and eye irritation in animals and did not induce skin irritation in human volunteers. Data were insufficient to determine the respiratory irritation potential of DEHP. In animal studies, DEHP was not a skin sensitiser and limited data indicated no sensitisation reactions in humans. Human studies indicated correlations between the risk of bronchial obstruction and plasticiser-emitting components of the indoor environment. However, there was insufficient evidence supporting a causal relationship between respiratory effects and DEHP.
- The repeated dose toxicity of DEHP was evaluated in a number of animal species, in both short-term (few weeks) and life-time studies by several routes of exposure. The most pronounced effects were on the liver (hepatomegaly, peroxisome proliferation), kidney (increased organ weights, mineralisation of renal papilla, tubule cell pigmentation and chronic progressive nephropathy) and testes (atrophy, vacuolated Sertoli cells, multinucleated gonocytes, Leydig cell hyperplasia).
- Exposure to DEHP during gestation and sensitive age post-natal periods in rodents also caused significant effects on reproductive parameters and development.
- Liver effects were reported in several rodent species. In a dietary study in rats fed with DEHP (at dose levels up to 939 mg/kg bw/d), hepatotoxicity was indicated by significant increases in serum albumin, absolute and/or relative liver weights and peroxisome proliferation at 146.6 mg/kg bw/d and above. The NOAEL for these effects was 28.9 mg/kg bw/d. A similar NOAEL, 25 mg/kg bw/d, was established based on hepatic changes after sub-chronic intravenous exposure in rats. The liver effects induced by oral administration of DEHP in rodents were not reported in oral administration studies with marmoset monkeys.
- DEHP-associated toxicity was consistently observed in kidneys of rats and mice. A LOAEL for these effects was established at 146.6 mg/kg bw/d from a 104-week rat dietary study, based on increased absolute and relative kidney weights.

Mineralization of renal papilla, tubule cell pigmentation and chronic progressive nephropathy were observed at higher doses. The NOAEL for kidney effects was 28.9 mg/kg bw/d. No information related to kidney toxicity was available in monkeys. Human studies on DEHP-induced toxicity to kidneys were not available. The mechanism of DEHP-related toxicity to kidneys was not clear but it appeared that it was not related to peroxisome proliferation as kidneys lesions were found in both PPARa-null and wild-type mice. Given the lack of information on DEHP-induced kidney toxicity in primates (including humans), the relevance to humans of kidney effects observed in rats could not be excluded.

- Testicular toxicity of DEHP in repeated dose studies in rats manifested as decreased testes weights and testicular atrophy, increased bilateral aspermatogenesis, immature or abnormal sperm forms, seminiferous tubular degeneration, Sertoli cell vacuolation or complete loss of spermatogenesis. In a 13-week rat dietary study, a LOAEL of 37.6 mg/kg bw/d was established based on an increased incidence of Sertoli cell vacuolation. Significantly decreased absolute and relative testicular weights, mild to moderate seminiferous tubule atrophy and Sertoli cell vacuolation were observed at higher doses. The NOAEL was 3.7 mg/kg bw/d.
- The consistent finding of testicular effects in rats and mice was in contrast to evidence from studies in marmosets where no significant treatment-related changes in testicular histology or more gross parameters were observed from oral exposures to DEHP at doses up to 2500 mg/kg bw/d. However the number of studies were limited and may not cover critical windows for testicular toxicity especially in young and developing animals.
- Therefore, although there were no reports of DEHP-induced testicular toxicity in primates, the relevance to humans of the effects observed in rats could not be excluded based on the plausible mode of action.
- DEHP was tested in a variety of short-term genotoxicity assays with predominantly negative results. Overall, DEHP was regarded as non-genotoxic.
- Carcinogenicity studies in rodents indicated significant dose related increases in hepatocellular and Leydig cell tumours. The LOAEL for tumour induction (hepatocellular neoplasms and mononuclear cell leukaemia [MCL]) in male rats was 147 mg/kg bw/d. The NOAEL was 28.9 mg/kg bw/d in males. The evaluator asserted that the mechanism by which DEHP and other peroxisome proliferation induce hepatotoxicity and hepatocarcinogenicity in rodents were regarded as not relevant to humans. Similarly, MCL was well known to occur spontaneously with high incidence in F344 rat strains and rare in other rat strains. This neoplasm was not found in other mammalian species and had no histological comparable tumour type in humans. Therefore the evaluator has asserted that DEHP induced MCL observed in rats was not considered relevant to humans.
- In a lifelong exposure study, DEHP was administered in the diet at 30, 95 and 300 mg/kg bw/d to male rats. At the highest dose increased incidences of hepatocellular adenomas and carcinomas were observered. Similarly, the incidence of benign

Leydig cell tumours in the highest dose group was 28 per cent; almost twice the incidence in the control group (16 per cent). The NOAEL for both liver and testicular carcinogenic effects was determined to be 95 mg/kg bw/d. The evaluator indicated that given the similarities in regulatory pathways within the hypothalamic-pituitary-thyroid (HPT) axis of rats and humans, the chemicals which induced Leydig cell tumours in rats by disrupting regulatory mechanisms within the HPT axis were likely to have similar effects in humans. However, the susceptibility of humans to hyperplasia and tumours may be less than rodents, as human Leydig cells were less sensitive to the proliferative effects of luteinizing hormone.

- In a prenatal developmental toxicity study, 0.025, 0.05, 0.10 and 0.15 per cent DEHP were administered to mice throughout gestation. Reduced maternal body weight gain was noted at 0.10 per cent and above, mainly due to reduced gravid uterine weight. Increased resorptions, late foetal deaths and malformed foetuses, and decreased foetal weight and viable foetuses were observed at 0.10 per cent and above. Increased malformed foetuses were seen also at 0.05 per cent and above. The external malformations included unilateral and bilateral open eyes, exophthalmia, exencephaly, and short, constricted or no tail. Visceral malformations were localised predominantly in the major arteries. Skeletal defects included fused and branched ribs and misalignment and fused thoracic vertebral centra. The NOAEL for maternal toxicity was 91 mg/kg bw/d (0.05 per cent) and for developmental toxicity was 44 mg/kg bw/d (0.025 per cent).
- In another prenatal developmental toxicity study, DEHP at doses of 40, 200, or 1000 mg/kg bw/d was administered by gavage to pregnant mice (15/group) from gestation day 6 to 15. At gestation day 17, decreased viable pups and increased resorptions and post-implantation loss were observed at 1000 mg/kg bw/d. Cardiovascular abnormalities, tri-lobed left lungs, fused ribs, fused thoracic vertebral centres and arches, immature livers and kidney anomalies were also observed at this dose. At 200 mg/kg bw/d, there was a slight increase in foetuses with intra-muscular or nasal haemorrhage or dilated orbital sinuses. There also were a small number of foetuses with anomalous innominate or azygous blood vessels at this dose level. A NOAEL of 200 mg/kg bw/d was established for maternal toxicity and 40 mg/kg bw/d for developmental toxicity.
- In another postnatal developmental study (rats exposed to DEHP during gestation and lactation), a NOAEL for developmental toxicity was established at 1.2 mg/kg bw/d, based on increased testes weight in prepuberal rats at 5 mg/kg bw/d. These weight increases were not associated with any histopathological or biochemical alterations. In a continuation of the study, a NOAEL for female developmental toxicity was established at 5 mg/kg bw/d, based on a significant delay in vaginal opening observed at 15 mg/kg bw/d in female offspring.

<u>Effects observed in humans</u>

- In humans, a number of studies have been conducted examining correlations between maternal mono(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP) levels and gestation length, onset of puberty and anogenital distance (AGD). Overall, these studies did

not provide convincing evidence of developmental effects from DEHP exposure in humans. This was related to the low power of studies due to small sample size, non-representative sample (usually one study centre) and uncertainties about the significance of the measured endpoints, for example AGD, as an indicator of developmental toxicity in humans.

- In a case report, three preterm infants artificially ventilated through PVC respiratory tubes developed unusual lung disorders resembling hyaline membrane disease during the fourth week of life. One infant died two weeks after birth, the other two were healthy at follow-up 20 months later. DEPH was detected in the lung after autopsy of the infant who died. The estimated inhalation exposure in the three infants ranged between 1 μg/h to 4,200 μg/h based on the concentrations of DEHP in the condensate collected from the water traps of the respirator tubing. However, this was likely to be an over-estimate as infants were not exposed to the condensate. DEHP, but not monoethylhexyl phthalate (MEHP), could be detected in urine samples.
- A mortality study carried out on 221 workers in a German plant producing DEHP reported eight deaths (including one carcinoma of the pancreas and one bladder papilloma). These workers had been exposed to DEHP for three months to 24 yr (average 11.5 yr). No information about exposure levels were provided; however, in two other reports by the same group, exposure levels in the plant ranged from 0.01 mg/m^3 to 0.16 mg/m^3.
- Occupational exposure to PVC and other products in the plastics industry was assessed in a case-control study of testicular cancer using self-administered questionnaires (148 cases and 315 controls). An increased risk of testicular cancer was observed (as evaluated by an increased odds ratio (OR) of 6.6; 95 per cent confidence interval: 1.4 - 32) for exposure to DEHP plasticised PVC, but not for other types of plastics. It was assumed that a potential oestrogenic effect of the chemicals used as plasticizers for PVC may have resulted in increased risk of testicular cancer. The evaluator, however, asserted that considering the design of the study (self administered questionnaires and occupational exposure to a number of different chemicals used in association with PVC plastics), no link could be established between testicular cancer and DEHP. This study was followed up by a larger case-control study taken from the Swedish Cancer Registry during 1993 - 1997. A total of 791 matched pairs completed a questionnaire regarding exposure. Overall exposure to PVC plastics gave an OR of 1.35 (confidence interval = 1.06 - 1.71). No dose-response relationships were found. There was no clear association between testicular cancer and exposure to PVC.
- Another study measured DEHP and MEHP concentrations in the plasma and peritoneal fluid of 35 women identified by laparoscopy as having endometriosis. There was no difference in the proportion of surgical patients compared to control women with detectable DEHP or MEHP (91.4 per cent compared to 92.6 per cent respectively). There was a significant difference in the median concentration of DEHP in the patients compared to control women (0.57 μg/mL compared with a control value of 0.18 μg/mL) but no difference in median MEHP concentration.

- In another study of endometriosis, plasma phthalate levels in 85 infertile women with endometriosis were compared with levels in 135 age-matched fertile control women undergoing laparoscopic sterilisation in the same hospital. Mean plasma DEHP levels in women with endometriosis were at least 3 times higher than levels in the controls. Differences were statistically significant.
- In a gonadotrophins study the gonadotropins and gonadal hormone levels of 74 male workers exposed to elevated levels of di-n-butyl phthalate (DBP) and DEHP in a PVC factory were measured. Urinary monobutyl phthalate (MBP) and MEHP levels (normalised to creatine) were significantly higher in exposed workers compared with 63 controls (MBP 644.3 μg/g versus 129.6 μg/g; MEHP 565.7 μg/g versus 5.7 μg/g). Circulating testosterone was significantly lower in exposed workers (8.4 μg/g) versus control workers (9.7 μg/g) and was negatively correlated with MBP and MEHP.
- In a reproductive toxicity study, blood phthalate levels in 41 premature thelarche patients (beginning of breast development without other sexual development signs) and 35 controls were compared. There was a statistically significant difference in average blood DEHP levels. DEHP was detected in 25 of the samples from premature thelarche patients at a mean concentration of 450 μg/L (187 - 2098 μg/L), MEHP concentration ranged from 6.3 to 38 μg/L. DEHP was detected in 5 of 35 blood samples from control patients at a mean concentration of 70 μg/L (276–719 μg/L). The reported levels in the control group were unusually high compared with the background MEHP concentration in urine in the normal population (mean 4.27, range 3.80–4.79 μg/L) and may reflect patient exposure to medical procedures within the hospital. A Member noted that this comparison may be invalid, unless the blood/urine relationship was known.
- In another reproductive toxicity study, cord blood samples were collected from 84 consecutive newborns (including a set of twins) delivered at an Italian hospital. DEHP and/or MEHP were detected in 74 of 84 cord blood samples with a mean (range) DEHP cord blood serum concentrations of 1.19 (0–4.71) μg/mL and MEHP of 0.52 (0-2.94 μg/mL). Mean gestational age, but no other parameter, was significantly lower in MEHP-positive neonates (38.16 weeks) versus MEHP-negative neonates (39.35 weeks). However, the levels measured in blood were unusually high compared to other studies.

Observed effects in humans – Evaluator's conclusion

- The evaluator concluded that a number of human reproductive toxicity studies have attempted to link maternal MEHP levels with gestation length, onset of puberty and AGD. These studies, however, did not show effects of DEHP exposure on developmental parameters.

Toys and child care articles – Exposure and Risk

The PEC report identified that the two dominant routes of exposure to DEHP through the use of plastic toys and childcare articles were:

- dermal exposure during normal handling of toys and childcare articles. Absorption via the dermal route, however, was significantly low; and
- oral exposure during intentional or inadvertent chewing, sucking and biting of these products. The PEC report estimated that a six-month old infant would absorb 27.8 µg/kg bw/day of DEHP at typical exposure conditions and 231 µg/kg bw/day at worst-case exposure conditions. This was based on studies which demonstrated that 6 month old infants were within an age range showing maximum mouthing behaviour, and have the lowest body weight in this age range.

Risk estimates take into account the likelihood for renal and reproductive effects at future life stages related to long term exposure through repeated handling and mouthing of toys. The MOE estimated from the internal DEHP dose in children and the dose at which no adverse effects were observed on the kidneys or the reproductive systems in animal systems was:

Toxicity	**NOAEL mg/kg bw/d**	**MOE for typical scenario exposure**	**MOE for worst case scenario exposure**
Reproductive	4.8	157	20
Kidney	28.9	950	120

The reproductive NOAEL used for this estimate came from a three-generational dietary study with rats for male developmental toxicity.

The risk estimates for kidney toxicity, in both scenarios of toy use by children derived MOEs above 100 and hence indicateed low risk of adverse effects on kidneys. The risk characterisation for DEHP exposure of children from use of toys and childcare articles indicated that under typical conditions of toy use the MOE for children for reproductive toxicity was marginally above 100. However, the MOE for the worst case scenario was significantly less than 100 indicating a risk of adverse effects in this scenario.

NICNAS sought to manage this risk by recommending to ACCC that it consider appropriate regulatory measures to limit exposure to DEHP resulting from the use of DEHP toys and child care articles.

Cosmetics – Exposure and Risk

The main route of exposure to DEHP from use of cosmetics was through dermal contact. Inhalation exposure was also possible from products applied as aerosols. Oral exposure was considered negligible as available information did not indicate use of phthalates in products most prone to accidental ingestion, such as toothpastes, mouthwashes, lipsticks and lip-glosses. The potential risks from cosmetic use were related to long term exposure through repeated use, especially of leave-on products, such as nail polish and face cream.

The evaluator indicated that due to lack of sufficient data on the cosmetic use pattern, conservative plausible assumptions had been used to determine the risks to consumers.

The potential risks from cosmetic use were related to long term exposure through repeated use, especially of leave-on products. The internal dose of DEHP from daily use of various DEHP-containing cosmetic products was estimated to be 154.7 µg/kg bw/d considering a "worst-case" scenario of daily use of all (leave-on, wash-off and spray application) cosmetic products. Additional assumptions were as follows:

- DEHP content in cosmetics was similar to that reported for DEP (diethyl phthalate) in a limited number of cosmetic products in Australia.
- Bioavailability of DEHP via the dermal route was 5 per cent and via the inhalation route was 100 per cent.

Calculated MOE for critical health effects of DEHP from estimated aggregate exposure to cosmetic products for the general population were:

Type of toxicity	**NOAEL mg/kg bw/d**	**MOE for reasonable worst case exposure scenario**
Reproductive	4.8	31
Kidney	28.9	187

The estimated margin of exposure (MOE) for reasonable worst case exposure scenario for reproductive toxicity was less than 100 in children and marginally above 100 for the general population. The evaluator therefore indicated that the risk of reproductive toxicity from simultaneous use of multiple cosmetic products containing DEHP for children and the general population was high.

The risk estimate for chronic effects to kidneys derived a MOE above of 187 indicating low concern for kidney toxicity in the general population using multiple cosmetic products containing DEHP.

Exposure to DEHP from use of personal care products was also estimated specifically for children. Based on these estimates MOE for reproductive effects of DEHP exposure was found to be below and marginally above 100. The calculated MOE for reproductive effects of DEHP for children was:

Infant Age	**Dose**$_{int,derm}$ (µg/kg bw/day)	**MOE**
Newborn	61.7	77
6 months	48.2	99
12 months	42.9	105

NICNAS therefore recommended banning DEHP for cosmetic use through Appendix C. No suggestion was made regarding any potential for a low concentration cut-off.

Other uses – Exposure and Risk

Members noted that industry use of DEHP was widespread, including as a plasticiser for PVC and polymers for coatings. Plasticised containers for cosmetic and personal care products may represent a source of exposure to phthalates, including DEHP, through leaching of plasticiser from the container into the product. The evaluator, however, stated that currently there were no data available regarding this issue.

DEHP leaching from PVC storage bags and tubing for medical use indicated that PVC used in medical devices contains a relatively high proportion (20 to 40 per cent) of plasticiser. The mean levels of DEHP reported in blood or blood products stored in DEHP containing PVC bags ranged from 0 μg/mL to 650 μg/mL, depending on storage conditions, duration of storage and blood product stored. The highest content of 650 μg/mL was detected in platelet concentrate supernatant stored in PVC bag for 42 d at 4^{o}C. The DEHP content extracted from drug formulations stored in plasticised PVC ranged from 0.2 μg/mL to 54.64 μg/mL, varying significantly depending on the contact area, temperature and storage conditions. The highest DEHP concentrations were reached when multiple lipophilic drugs were pre-mixed in intravenous fluid bags and agitated for 1 h.

Hazard Classification

Undiluted DEHP, for occupational purposes, was classified as a reproductive toxicant Category 2 requiring the Risk phrases R60: *May impair fertility* and R61: *May cause harm to the unborn child* in the Australian Hazardous Substances Information System (HSIS) of Safe Work Australia. These risk phrases apply to products containing more than 0.5 per cent DEHP.

February 2011 Pre-meeting Submissions

XXXXX

The submission advised that an interim ACCC ban on children's plastic products with more than 1 per cent DEHP came into effect on 2 March 2010. The submission further indicated that the interim ban would become a permanent ACCC ban, expected by March 2011.

The submission asserted that the delegate's proposed limit of 0.05 per cent DEHP in respect to toys and childcare articles was inconsistent with the ACCC's ban on such goods containing more than 1 per cent DEHP. It was asserted that restricting the use in toys and childcare articles to less than 0.05 per cent DEHP would raise significant compliance issues with suppliers, and cause safety concerns amongst consumers regarding these products. The submission asserted that the ACCC's restriction on DEHP reflects industry concern regarding the ban.

XXXXX

XXXXX made a pre-meeting submission. This mainly reiterated the PEC report and XXXXX pre-meeting submission.

The submission asserted that determination of the level of exposure to DEHP from cosmetics high risk subpopulations was difficult. The results of the large biomonitoring studies show that female adults had maximum exposure levels. This raised concerns that the high exposure scenarios with MOEs extremely close to or below 100 may be applicable to the subpopulation most at risk for reproductive developmental effects in their progeny i.e. pregnant and breastfeeding women. Similarly, for young children undergoing critical developmental processes there was concern regarding reproductive developmental toxicity from potential DEHP exposure through use of lotions and creams.

Reiterated that risks arising from uses other than in cosmetics and toys and childcare articles were not considered in the NICNAS PEC Report. The submission noted that the undiluted form of DEHP met the Schedule 7 criteria, based on "a severe hazard from repeated and unprotected use or a significant risk of producing irreversible toxicity, which may involve serious acute or chronic health risks or even death if it is inhaled, taken internally or penetrates the skin". The submission further noted, however, that the impact of listing DEHP in Schedule 7 for uses other than cosmetics may require further consultation.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that relevant matters under Section 52E(1) included (a) risks and benefits; (b) the purpose and extent of use; and (c) toxicity of a substance.

Members discussed whether there was merit in prohibiting the use of DEHP in cosmetics. Members agreed that although DEHP's acute toxicity was low, significant concerns existed with regard to reproductive toxicity, should exposure occur. It was generally agreed that the PEC report's approach in establishing MOEs below 100 for exposure through cosmetic use was sufficiently concerning as to warrant consideration of a prohibition through scheduling. Another Member noted that there were a number of international precedents for such an action. Members agreed that an Appendix C entry for cosmetic use of DEHP was appropriate.

Members then considered whether there should be a low concentration cut-off from the Appendix C entry to allow for unintended contamination. Members noted advice that there had been a few cross-contamination incidences involving small amounts of DEHP inadvertently leaching into cosmetic products during the manufacturing process. These incidences were usually reported from multi-product manufacturing plants. Members agreed, however, that this was a good manufacturing practices issue rather that a matter needing to be addressed through scheduling. In addition, a Member was concerned that setting an Appendix C cut-off would in turn imply that deliberate use up to that cut-off was acceptable, contradicting the Committee's intent that DEHP should not be an ingredient in cosmetics at any level. Members agreed that there was insufficient

information at this time to allow the setting of a low concentration cut-off from the Appendix C entry for cosmetic use of DEHP.

Members, noting the intent of the ACCC's ban for use of DEHP in certain children's products to become a permanent ban, also considered whether a similar restriction needed to be implemented through scheduling. Members generally agreed that regulation of these types of products was normally best done through the ACCC's mechanisms. It was also noted that most toy manufacturers, given the nature of their business, would tend to be more aware of the ACCC controls. In addition, the ACCC had better recall powers should breeches occur. Members agreed that it was not appropriate to duplicate the ACCC controls through scheduling.

Some Members additionally raised concern as to whether the ACCC's ban was sufficiently protective, as the EU had imposed a more than 0.1 per cent ban (versus the ACCC's 1 per cent cut-off). A Member was also concerned that, as the EU's cut-off was significantly lower than that for Australia, it was possible that toy manufactures in countries without DEHP controls could see Australia as a "dumping ground" for those products they were not able to export to the EU. Members noted advice from NICNAS that the reason for the ACCC's 1 per cent cut-off was based on conservative scenario calculations which indicated that this level of DEHP would result in a MOE of 860, a significant safety margin in protecting the health and safety of children. It was noted that the EU cut-off may in fact be too conservative. Members generally maintained, therefore, that ACCC remained the appropriate authority for considering this aspect of controls for DEHP. It was agreed that concerns arising from the difference between the ACCC's and overseas cut-offs for DEHP in children's products was a matter for ACCC to consider and resolve.

Members then discussed whether there was a need to create a parent entry for DEHP. Members noted that while the hazard from undiluted DEHP may be indicative of a Schedule 7 entry, the question was whether there was an actual risk necessitating such scheduling action, particularly given the wide spread use and potential for regulatory impact of such a move. In this regard a Member was particularly concerned about the lack of submissions from the affected industries. The Member stated that it was possible that these industries were not aware that scheduling could impose controls on articles containing scheduled poisons.

Members noted that, according to the PEC, exposure to DEHP in articles required a mechanical force to release the DEHP (i.e. children chewing on toys). Members therefore agreed that any leaching risk from products, other than those already identified by ACCC, would be very low. Members also noted that it currently appeared that undiluted DEHP only had industrial uses. It was noted that Safe Work Australia listed DEHP in its Australian Hazardous Substances Information System and Members agreed that it appeared reasonable, on the current available data, that the consequent Occupational Health and Safety controls on workers handling DEHP were sufficiently protective as to not warrant additional measures through scheduling. The Members agreed that a parent entry was not necessary based on current use patterns of DEHP.

A Member raised some concerns regarding medical use of DEHP, such as colostomy bags, where patients could be exposed to significant concentrations (up to 40 per cent) of DEHP. The Member indicated that these bags have to be attached to patients for 24 hours a day over a life span and this continual exposure and potential uptake of DEHP was concerning. Another Member noted that such exposure, if any, would depend on the type of colostomy bag, as many are attached in such a way that would minimise dermal contact. Members agreed that DEHP, when used in medical devices, was a TGA regulatory issue rather than a scheduling matter. It was noted that TGA, in consultation with other international agencies, had already commenced investigations regarding DEHP in medical devices. Members agreed, however, that it was still appropriate to recommend that the delegate advise TGA of the need to review concerns from the potential leaching of DEHP when used in some medical devices.

Implementation date

Members discussed whether there was a need to allow additional time for the cosmetic industries to respond to the prohibition of DEHP from their products. A Member asserted that this was a significant change and that affected industries may need to reformulate. Other Members noted that the Committee had considered the risk from exposure to DEHP via cosmetic use to be serious enough to warrant an Appendix C entry, so it followed that this risk was also serious enough to require implementation without additional delay. The Committee agreed that an implementation timeframe of six months appeared appropriate.

DELEGATE'S DISCUSSION

The delegate concluded that the recommendations of the ACCS were clear and appropriately supported. The delegate also agreed that an implementation period of six months was appropriate.

The delegate also noted that the NICNAS published information regarding its controls on cosmetics clearly advised that a cosmetic included personal care / toiletry preparations i.e. a substance or preparation intended for placement in contact with any external part of the human body with a view to altering the odours of the body; or changing its appearance; or cleansing it; or maintaining it in good condition; or perfuming it; or protecting it.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits (b) the purpose and extent of use and (c) toxicity of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include use of diethylhexyl phthalate in cosmetic products in Appendix C.

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that use of diethylhexyl phthalate in cosmetic products be included in Appendix C. The delegate also confirmed an implementation date of 1 January 2012.

APPENDIX C – New Entry

DIETHYLHEXYL PHTHALATE for cosmetic use.

1.4 EMODEPSIDE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of emodepside and decided to seek advice from the ACCS on the following:

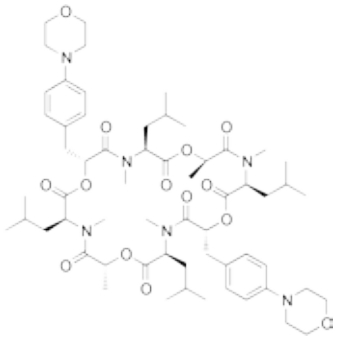
Emodepside – proposal to amend the Schedule 5 entry for emodepside by extending the current capture of preparations containing 2.5 per cent or less of emodepside for external treatment of animals to also capture preparations containing 2.5 per cent or less of emodepside for oral treatment of animals.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the Schedule 5 emodepside entry be broadened to also capture oral animal treatments containing 30 mg or less of emodepside per dosage unit. The Committee also recommended an implementation date of no more than 6 months after the delegate's final decision.

BACKGROUND

Emodepside is a pyrazino-isoquinoline, a semi-synthetic derivative of PF1022A, a cyclic octadepsipeptide, originally derived from the plant fungus *Mycelia sterilia*. The structure of emodepside is:



Emodepside achieves its anthelmintic action by interaction with the latrophilin receptor. These receptors regulate the release of neurotransmitters, such as amines and neuropeptides. Emodepside acts at the neuromuscular junction by stimulating presynaptic receptors belonging to the secretin receptor family, resulting in a post-synaptic ion influx leading to inhibition of pharyngeal pump function, ultimately leading to paralysis and death of the parasite.

In June 2005, the National Drugs and Poisons Schedule Committee (NDPSC) noted advice regarding an application to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking approval of the new active ingredient emodepside, and registration of a product range containing 2 per cent emodepside. The products were topically applied liquids. The NDPSC agreed that, on the basis of its toxicity profile, emodepside for animal use be included in Schedule 6 with a cut-off to Schedule 5 at 2.5 per cent or less for external treatment of animals.

In June 2006, the NDPSC noted a number of editorial changes and errata, including rephrasing of the Schedule 5 emodepside entry from "…in preparations for external treatment of animals containing 2.5 per cent or less of emodepside" to "…in preparations containing 2.5 per cent or less of emodepside for external treatment of animals".

XXXXX has submitted data to the APVMA in support of a new oral product XXXXX.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a rescheduling recommendation for emodepside. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Emodepside is currently in Schedule 6 for the treatment of animals with a cut-off to Schedule 5 for preparations containing 2.5 per cent or less of emodepside for external treatment of animals.

INITIAL SUBMISSIONS

Applicant's Submission

The XXXXX Report found that the toxicological profile of emodepside in preparations for oral administration containing 2.5 per cent or less of emodepside was consistent with the criteria for a Schedule 5 listing (noting Schedule 5 is currently limited to external treatment of animals i.e. oral animal products are Schedule 6). The evaluator recommended that the current Schedule 5 entry for emodepside be amended accordingly by deleting the phrase "for external treatment of animals".

XXXXX.

Members noted that the data package provided in the submission comprised one emodepside short-term repeat-dose oral toxicity study in XXXXX and one pharmacokinetic study on emodepside in XXXXX. These studies were GLP-compliant and contribute to the toxicological profile of emodepside.

Toxicology – Technical Grade Active

Members noted that XXXXX had previously evaluated emodepside and a toxicological profile had been established, as summarised below:

- Absorption, distribution, metabolism and excretion: Incompletely absorbed from the gastrointestinal tract, with XXXXX. The bioavailability was calculated as XXXXX. Excretion was initially rapid, followed by a slow decline phase. The potential for accumulation was considered high, based on a slow elimination from the plasma XXXXX. The compound was highly lipophilic.
- Acute toxicity: Low acute oral and dermal toxicity. XXXXX. Emodepside was a non-irritant to the eye and skin of XXXXX, and was not a skin sensitiser in XXXXX.
- Repeat-dose effects: Studies in XXXXX showed that the primary organs affected were the liver and kidneys, with effects on the endocrine system (glucose regulation and possibly the female reproductive system) and the neurological system. XXXXX. Studies in XXXXX did not reveal specific organ toxicity, though tremor and unsteady gait were potentially indicative of neurotoxic effects. A short-term (~4 week) oral NOEL was established at between XXXXX.
- Genotoxicity: Emodepside was neither mutagenic nor clastogenic in a range of *in vitro* and *in vivo* assays. In developmental studies in XXXXX, emodepside caused developmental toxicity evident predominantly as retarded ossification from XXXXX, a dose that did not cause maternal toxicity. Therefore, a XXXXX maternal NOEL was established at XXXXX, and a foetal developmental NOEL was established at XXXXX. In XXXXX there was a slight increase in the incidence of a common cardiac malformation, as well as retarded ossification. A XXXXX maternal NOEL was established at XXXXX, and a foetal developmental NOEL was established at XXXXX.

- Neurotoxicity: Although emodepside acts as an anthelmintic by causing paralysis, in mammals neurotoxicity appears predominantly excitatory. Evidence of neurotoxicity in repeat-dose studies was seen in XXXXX, but not XXXXX. Clinical signs suggestive of effects on the nervous system include uncoordinated or staggering gait, changes in motility, head tilt and tremor.

Toxicology – Product XXXXX

No toxicological studies on the formulated product were provided. The acute toxicity of the products was estimated using available toxicological information, and is summarised as follows:

Toxicity end point	**Toxicity of Product**
Oral	Low toxicity
Dermal	Low toxicity
Inhalational	Likely to be low toxicity
Skin and eye irritation	Not irritating
Skin sensitisation	Not sensitising

- The product was predicted to be of low acute oral and dermal toxicity. It was predicted to be non-irritating to skin and eye, and non-sensitising to skin. Insufficient acute inhalational toxicity data was available for the constituents in the product formulation, though it was likely to be of low acute inhalational toxicity based on the product formulation.

Comparison of External and Oral Product Risks

Previous advice to the 2005 NDPSC meeting asserted that the toxicity profile of emodepside was consistent with inclusion in Schedule 5 with the notable exception of its acute oral toxicity in XXXXX. However, the toxicity profile of an external product (~2 per cent emodepside) indicated that the acute oral LD_{50} was greater than XXXXX, consistent with inclusion into Schedule 5.

XXXXX.

- The concentrations of emodepside XXXXX in the oral formulation are similar to that found in the previous external formulation. XXXXX. The moderate eye irritation observed in the external formulation is likely to be attributable to non-active constituents, as XXXXX emodepside XXXXX have been shown in animal studies to be non-irritants to the eye.
- The XXXXX Report therefore proposed that the toxicity profile of the oral product was similar to that of the external product, and that the oral formulation had a toxicity profile consistent with inclusion in Schedule 5.

Use Pattern / Exposure

- XXXXX. The main route of exposure would be dermal, XXXXX. XXXXX suggested that the risk of residue was likely to be low, and hence dermal or ocular exposure to residue would also likely be low. Furthermore, skin and eye irritation and skin sensitisation risks were expected to be very low.
- As the product would be used in a domestic situation, the accidental oral ingestion exposure was considered. A conservative scenario where ingestion of XXXXX by an adult or child over a 24-h period was considered, noting that the possibility of multiple XXXXX ingestion was heightened by the enhanced palatability due to XXXXX. Assuming the average child weight of 10 kg, this would be equivalent to an exposure of XXXXX. Comparing this exposure with the acute oral toxicity indicated that the risks associated with accidental oral ingestion were likely to be low.
- Veterinarians and veterinary support staff using the product may be exposed to the XXXXX form by the dermal route when dispensing to animals. It was expected that occupational users would have similar exposure patterns to that for the general public.
- Post-application exposure was expected to be limited to dermal-to-oral transfer of residue from unwashed hands, and potential exposure to unabsorbed emodepside in faecal matter (up to XXXXX of the administered oral dose), due to the moderate oral bioavailability of emodepside.

Hazard Classification

Emodepside was not listed in Safe Work Australia's Hazardous Substances Information System Database. The evaluator recommended classification of emodepside as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances, with the following risk phrase "*Harmful if swallowed*" for concentrations greater than 2 per cent.

XXXXX.

Applicant's Response to the Evaluation Report

XXXXX had considered the XXXXX Report, including the scheduling recommendation, and accepted the XXXXX proposal for scheduling.

February 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that relevant matters under Section 52E (1) included (a) risks and benefits; (b) the purpose and extent of use; and (c) toxicity.

Members noted that there appeared to be no basis in the new data to support any reconsideration of the 2005 NDPSC decision to create a Schedule 6 parent entry for emodepside. It was agreed that the only issue to be considered at this time was the potential broadening of the current external animal use low concentration cut-off to Schedule 5 to also incorporate low concentration oral preparations.

A Member noted some developmental effects but observed that the level of inadvertent dermal exposure to the oral product would be small. Similarly the neurotoxic effects only occurred at high doses and were unlikely to be an issue from inadvertent dermal exposure to the oral product.

A Member also noted that these effects had previously been considered when the NDPSC determined that a Schedule 5 cut-off was appropriate for external animal preparations containing 2 per cent or less of emodepside. In response to a Member's concern that the oral presentation for animal use was likely to be palatable to children, it was noted that the product would be in child-resistant packaging.

Members generally agreed therefore that the data supported a broadening of the current cut-off from the Schedule 6 parent entry.

Members noted, however, that while the submitted data indicated a minimal risk from low concentration oral emodepside, this data was not direct product data. Members agreed therefore that it would be appropriate to limit consideration to a cut-off to Schedule 5; a consideration of an exemption from the requirements of scheduling would not be appropriate.

Members also discussed whether the cut-off to Schedule 5 should be broadened generally to all low concentration presentations of emodepside, or whether this should be limited to specific presentations. Members noted advice that there was potential for emodepside to present as an injectable, and agreed that there was insufficient data at this time to extend the cut-off to such use. Members agreed that the cut-off to Schedule 5 should therefore be limited to oral animal use, in addition to the existing external animal use cut-off.

Members then discussed the appropriate level of this cut-off. A Member noted that the data submitted had related to a solid dose oral presentation and asserted that it would be odd to suggest a percentage cut-off for such a presentation, noting that such a percentage could easily be manipulated. Several Members noted that it was more usual to set a scheduling cut-off based on a specified amount of emodepside per dosage unit, noting that the highest such amount addressed by the submitted data was 30 mg. The Members agreed that 30 mg per dosage unit was a suitable limit based on the currently available data.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACCS, including the recommendation for implementation without delay, were clear and appropriately

supported. The delegate agreed with these recommendations. The delegate further agreed that the intent of these recommendations was achieved through the revised wording proposed by the ACCS for the Schedule 5 emodepside entry.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) the purpose and extent of use; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate decided to broaden the Schedule 5 emodepside entry to also capture oral animal treatments containing 30 mg or less of emodepside per dosage unit. The delegate decided that an implementation date of 1 September 2011 was appropriate (i.e. three months after publication of the final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate decided to broaden the Schedule 5 emodepside entry to also capture oral animal treatments containing 30 mg or less of emodepside per dosage unit. The delegate confirmed an implementation date of 1 September 2011.

Schedule 5 – Amendment

EMODEPSIDE – Amend entry to read:

EMODEPSIDE in preparations:

(a) for external treatment of animals containing 2.5 per cent or less of emodepside; or

(b) for oral treatment of animals containing 30 mg or less of emodepside per dosage unit.

1.5 FLUMIOXAZIN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of flumioxazin and decided to seek advice from the ACCS on the following:

Flumioxazin – proposal to amend the Schedule 7 entry for flumioxazin to allow a cut-off to Schedule 6 for preparations in water soluble bags when individually packed in sealed sachets.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current scheduling of flumioxazin (Schedule 7 without any cut-offs) remains appropriate.

BACKGROUND

Flumioxazin is a N-phenylphthalimide herbicide and a porphyrin pathway inhibitor, and acts by reducing the enzyme activity of protoporphyrinogen oxidase (PPO). This is the penultimate enzyme in the synthetic pathway for chlorophyll in plants.

Inhibition of PPO in both animals and humans interferes with the haeme biosynthetic pathway that occurs in the mitochondria of the erythroblast haeme and leads to low levels of haemoglobin. Additionally, inhibition of PPO can lead to accumulation of porphyrins (predominantly protoporphyrin IX (PPIX)) in the red blood cells resulting in alterations of the cell membrane and haemolytic anaemia, while porphyrin accumulation in other tissues/organs such as the liver can cause organ damage.

In October 2002, flumioxazin was included in Schedule 7 without any cut-off because of irreversible developmental/reproductive effects observed at non-maternotoxic acute doses, chronic hepatotoxicity and induction of porphyria and the potential for photodermitis. This decision was confirmed in February 2003.

Other chemicals in the N-phenylphthalimide class include azafenidin and flumiclorac pentyl, which have similar toxicological profiles to flumioxazin and are both Schedule 7.

XXXXX has submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking the registration of XXXXX (water soluble packaging) XXXXX. The packaging was intended to reduce the risk of exposure to the product in order to address the hazards to human health, in particular the developmental/reproductive hazard, and to support re-scheduling of this formulation into Schedule 6 and XXXXX.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for flumioxazin. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Flumioxazin is currently included in Schedule 7.

INITIAL SUBMISSIONS

Applicant's Submission

The XXXXX Report found that flumioxazin, when in water soluble bags packed in sealed sachets, does not present a significant hazard to human health through reproductive/development effects, chronic liver toxicity or induction of porphyrias. The evaluator therefore recommended that flumioxazin remain in Schedule 7, but with a cut-off to Schedule 6 for preparations in water soluble bags when individually packed in sealed sachets.

The evaluator also recommend that flumioxazin:

- When in Schedule 7, be included in Appendix F with Warning Statement 47 '*WARNING – This product contains flumioxazin, which causes birth defects in certain laboratory animals. Women of childbearing age are advised not to mix, load or spray this product. They should keep out of crops being sprayed*.'
- When in Schedule 6, be included in Appendix F with Warning Statement 46 '*WARNING - Contains flumioxazin which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with flumioxazin*.'

Members noted that the evaluator was subsequently informed that Appendix F no longer applied to APVMA regulated uses (the APVMA instead sets this when approving labelling as part of its product approval process).

XXXXX

Members also noted the following summary from the XXXXX Report's toxicology discussion for flumioxazin:

- The ADI for flumioxazin was established in 2002 at 0.003 mg/kg bw/d derived from a NOEL of 3 mg/kg bw/d in an XXXXX, with a 1000-fold safety factor in view of the irreversible nature of the developmental effects and the fact that development of the fetus could be affected by a single dose.
- The ARfD for flumioxazin was established in 2002 at 0.03 mg/kg bw/d derived from a NOEL of 3 mg/kg bw/d in an XXXXX, with a 100-fold safety factor.
- No toxicological data were provided with the submission to APVMA; the Report relied instead on data from previous XXXXX evaluations (2002).

<u>Acute toxicity</u>

- These previous data indicated that flumioxazin:
  - Has low oral XXXXX, dermal XXXXX and inhalational toxicity XXXXX.
  - Was neither a skin irritant in XXXXX, nor a skin sensitiser in XXXXX, but it is a slight eye irritant in XXXXX.

Repeat Dose

- In mammals, PPO is a key enzyme in the haeme synthesis pathway. Hence, inhibition of PPO in animals and humans interferes with haeme synthesis, leading to haemoglobin deficiency (microcytosis and hypochromasia) and also reduction of liver cytochrome P_{450}. Decreased synthesis of the end products of the pathway causes upregulation of upstream products in the haeme pathway, resulting in increased porphyrin-intermediate production.
- Porphyrin accumulation in the red blood cells results in alterations in the integrity of the cell membrane and haemolytic anaemia. Porphyrin accumulation in the tissues/organs causes a variety of organ damage, in particular in the liver. Liver toxicity appeared to be a common indicator of effects induced by high doses of flumioxazin in XXXXX. Interference in metabolism and liver function, and altered liver enzyme activities corresponding to histopathological lesions in hepatocytes, bile duct and gall bladder may reflect porphyrin-related hepatocytic injury. XXXXX appeared to be the most sensitive species demonstrating a characteristic of a pattern of toxic effects indicative of PPO inhibition and associated disruption of the haeme biosynthetic pathway.
- The proposed mechanism of action (PPO inhibition) for repeat-dose toxicity in animals has biological relevance in humans. Porphyrias are known to occur in humans and are caused by deficiencies of enzymes of the haeme biosynthetic pathway or defects in porphyrin metabolism. They invariably result in excessive secretion of porphyrins and porphyrin precursors. XXXXX data demonstrated that the sensitivity of human liver mitochondria to flumioxazin induced PPO inhibition was similar to that of XXXXX, suggesting that XXXXX is an appropriate model for human toxicity in the risk assessment of flumioxazin.
- Flumioxazin showed neither genotoxic nor carcinogenic potential.

Reproductive Toxicity

- A reproductive study in XXXXX demonstrated effects of concern on reproductive indices in the absence of maternotoxicity in addition to effects on male reproductive organs.
- The NOEL was approximately XXXXX for maternotoxicity.
- The NOEL was approximately XXXXX for reproductive toxicity.

Developmental Toxicity

- Developmental toxicity was the major concern for flumioxazin. In XXXXX, developmental effects were induced by both acute oral and dermal administration on gestation days XXXXX, in the absence of maternotoxicity. Following oral and dermal doses, embryo/fetal loss and/or reduced fetal weight were observed in the presence of maternotoxicity XXXXX were also observed at maternotoxic doses.

- Increased incidence of cardiovascular abnormalities, XXXXX were observed below maternotoxic oral and dermal doses. The NOEL was XXXXX for embryo/fetal developmental toxicity following oral or dermal dosing, respectively.
- Flumioxazin did not produce developmental toxicity in XXXXX even at a maternally toxic oral dose.

Developmental Toxicity – mechanism

- In the 2002 application it was proposed that flumioxazin inhibited PPO in XXXXX embryos, thereby interfering with normal haeme synthesis, and resulting in clinical manifestations (i.e. anaemia) and dysmorphogenesis. The fetal anaemia may lead to hypoxia in fetal tissues followed by suppressed liver function and decreased protein synthesis which could result in wavy ribs and fetal oedema. Concurrently, the fetus would compensate for the anaemia by pumping a greater volume of blood, and thus would lead to an enlarged heart and consequently permanent heart damage.
- Mechanistic studies have been evaluated which supported this hypothesis.
- The weight of evidence from the available toxicological data for flumioxazin indicated that the teratogenic and/or fetotoxic mechanism of action for flumioxazin was via PPO inhibition following acute exposure during organogenesis, causing disruption of the haeme biosynthetic pathway resulting in clinical manifestations such as anaemia and dysmorphogenesis in the developing fetus. It was considered that the NOELs for developmental and reproductive effects at non-maternotoxic doses were threshold doses for these toxic endpoints. It has been noted that flumioxazin is structurally related to thalidomide which is a known human teratogen with no established threshold dose. However, there was no evidence of similarity in underlying pathogenesis (i.e. effects on angiogenesis/limb development) or similar molecular targets for flumioxazin.

Members additionally noted the following toxicology summary for the product:

- No toxicological data were provided with the submission, relying instead on data from previous XXXXX evaluations (2002) which assessed acute toxicity data for XXXXX.
- These previous data indicated that 50 per cent flumioxazin had low oral XXXXX, dermal XXXXX and inhalation toxicity XXXXX. It was a slight irritant to the eyes and skin of XXXXX, but is not a skin sensitiser in XXXXX.

Use Pattern / Exposure

- The products were not intended for domestic use. The major risk to the general public would be through exposure to residues in food. However, as the products are intended for use as XXXXX, it was considered that the potential for public exposure to pesticide residues in food was minimal. Maximum residue limits (MRLs) for flumioxazin in food commodities have been set at or about the limit of analytical quantification.

- There was potential for exposure to the public to flumioxazin in spray drift. However, this could be mitigated by good agricultural practice.
- XXXXX. Workers involved in the re-packaging of products will therefore be exposed to both active and non-active constituents of the products. Others involved in the transportation and sale of the packaged products could only become exposed if the packages were breached.
- Farmers, their employees and spray contractors will be the main users of these products. They may become contaminated with the products/spray when mixing and loading, during application, cleaning application equipment and entering treated areas. The main routes of occupational exposure will be dermal and inhalational, though ocular exposure may also occur when preparing and spraying the product.
- XXXXX will be in the form of XXXXX water soluble bags XXXXX. The water soluble bags will be individually packed in sealed foil sachets (made from aluminium lined polyethylene) that do not burst and do not disintegrate when exposed to water or the elements.
- As a result of the new presentation in water soluble packaging, it was unlikely that there would be acute oral or dermal exposure to the concentrated product. There was potential for accidental oral and/or dermal exposure to the dilute products/spray.
- Acute exposure to female workers exceeding XXXXX dermally would be of concern for developmental effects. This is based on a tolerable acute oral dose of 1.8 mg, and a tolerable acute dermal dose of 18 mg, estimated using a 100-fold safety factor and assuming a 60 kg bodyweight.
- With the Safety Directions for the products, including the use of PPE during mixing and loading and application (cotton overalls buttoned to the neck and wrist over normal clothing, a washable hat, chemical resistant gloves and face shield), it was considered unlikely that accidental exposure could exceed the tolerable acute oral or dermal dose for reproductive/developmental effects.
- There was a potential risk associated with repeat exposure to this product. Since the NOEL was derived from a repeat dose study in animals, a margin of exposure (MOE) of 100 or above was acceptable. The MOE takes into account both interspecies extrapolation and intraspecies variability. Mixing, loading and applying the products in water soluble bags without gloves, wearing long pants and long sleeved shirt (single layer of clothing) would be associated with total MOEs > 439. Despite the low quality of the data used in the estimation of exposure during mixing and loading, the large MOEs indicate that there was unlikely to be a risk associated with repeat systemic exposure to these products.
- Occupational risk assessment indicated that workers without gloves and wearing a single layer of clothing using flumioxazin products in water soluble bags in accordance with proposed use patterns were unlikely to reach systemic exposure levels that would be of concern for irreversible chronic liver toxicity or additional

repeat-dose effects associated with PPO inhibition such as the induction of porphyrias.

- Based on the limited possibility for post-application exposure a re-entry interval was not recommended. However, on the basis of the intrinsic developmental/reproductive toxicity of flumioxazin, the standard default re-entry statement was recommended: *Do not allow entry into treated areas until the spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and chemical resistant gloves. Clothing must be laundered after each day's use.*

Hazard Classification

Flumioxazin was listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database with the risk phrase (at concentrations of 0.5 per cent or more) '*May cause harm to the unborn child*'.

XXXXX

Applicant's Response to the Evaluation Report

XXXXX advised that XXXXX had considered the XXXXX Report, including the scheduling recommendation, and accepted the XXXXX proposal for scheduling.

February 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that relevant matters under Section 52E (1) included (a) risks and benefits; (b) the purpose and extent of use; (c) toxicity; and (d) the formulation, packaging and presentation.

Members generally agreed that the proposed packaging would result in a safer product that would reduce the risk of accidental exposure. The question was whether this mitigation of exposure risk was sufficient to allow use as a Schedule 6 poison.

A Member argued that, while reduced, there would still be some risk to workers using flumioxazin. The Member also noted that while this packaging would mitigate exposure at a single, although critical, stage (handling of the concentrated product when diluting it for spraying), the risks from all other stages of use would not be similarly mitigated (i.e. exposure of workers during initial production, or to the dilute spray during application). A Member advised that accidental exposure was more likely to occur when operators had to address faulty or blocked applicators. Another Member noted, however, that this would be exposure following dilution with an associated substantial decrease in risk (noting that the effects of concern were threshold effects). Members also noted advice

that the entire process, not just the preparing of the product for spraying stage, had been modelled in deriving the acceptable MOE.

A Member remained concerned that excessive exposure could still occur and, if exposed, the toxicity concerns would be identical to those that informed the original Schedule 7 decision. In particular, the Member asserted that inclusion in Schedule 6 greatly increased the potential for leakage / diversion, such as into the hobby farm sector or domestic garden use (acknowledging there was no intent by the sponsor to supply the product for such uses). The Member suggested that should such leakage occur, it would seem reasonably likely that some users would be tempted to breach the packaging in order to prepare a smaller batch for application on a limited area. The Member asserted that the need for compliance with the directions for use suggested that stringent labelling and restrictions associated with Schedule 7 were necessary.

A Member was also concerned that there could be a perception by some users that down scheduling to Schedule 6 suggested that flumioxazin was now less toxic, when this was not the case. It was reiterated that the packaging had not reduced the hazard; it had reduced the potential for exposure; hence, the risk. A Member also noted that Schedule 7 users were a skilled group of users, while supply as Schedule 6 would allow access by less skilled operators.

Members agreed that the new packaging was a positive step that would provide benefit to the safe use of flumioxazin in agricultural practice. Several Members argued, however, that this benefit was insufficient to outweigh the risks described above if Schedule 6 access were allowed. The Committee agreed that this packaging had great potential for increasing the current safety for skilled Schedule 7 workers, but that this was not sufficient to justify a Schedule 6 down scheduling.

DELEGATE'S INTERIM DISCUSSION

The delegate noted that the ACCS did not support the recommendation in the XXXXX Report to allow a cut-off for flumioxazin preparations packed in individual sealed foil water-soluble packages to Schedule 6.

The delegate noted that there was precedent in the SUSMP (e.g. abamectin, endosulfan and parathion-methyl Schedule 6 entries) where risk mitigation through a specific formulation (microencapsulation) or packaging (cattle ear tags) allowed for an exception from Schedule 7 to Schedule 6. There were also some similar exceptions from Schedule 6 to Schedule 5 based on risk minimisation associated with packaging.

The delegate agreed that risk mitigation had been adequately established for preparations in water soluble bags when individually packed in sealed sachets in the XXXXX Report through the estimated worker exposure, which resulted in an adequate MOE due to the significantly reduced risk of contact with the product in such packaging.

The delegate further noted that the Schedule 7 parent entry for flumioxazin was primarily driven by the risk of reproductive and developmental toxicity, while other aspects of the toxicity profile were more consistent with Schedule 6 scheduling. The delegate concluded that the lowered risk to product users associated with the sealed packages was adequately addressed through label warnings of the risk to women of child-bearing age.

The delegate noted the concern of some ACCS Members that there was potential for flumioxazin preparations, if allowed to be Schedule 6, to be diverted into user groups with less training or experience in handling toxic pesticides (e.g. hobby farms or domestic gardens). The delegate concluded that this concern was insufficient to warrant retaining flumioxazin preparations, when in water soluble bags when individually packed in sealed sachets, in Schedule 7 in light of the demonstrated risk mitigation afforded by the packaging.

The delegate acknowledged an ACCS Member's contention that the packaging did not reduce the hazard of the material, but it did mitigate the exposure potential, and hence the risk.

The delegate therefore decided to set-aside the ACCS recommendation and instead accepted the proposal to list flumioxazin preparations in water soluble bags when individually packed in sealed sachets in Schedule 6.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) the purpose and extent of use; (c) toxicity; and (d) the formulation, packaging and presentation.

DELEGATE'S INTERIM DECISION

The delegate decided to amend the Schedule 7 entry for flumioxazin to include a cut-off to Schedule 6 for preparations in water soluble bags when individually packed in sealed sachets. The delegate decided that an implementation date of 1 September 2011 was appropriate (i.e. three months after publication of the delegate's final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that the Schedule 7 entry for flumioxazin be amended to include a cut-off to Schedule 6 for preparations in water soluble bags when individually packed in sealed sachets. The delegate also confirmed an implementation date of 1 September 2011.

Schedule 6 – New entry

FLUMIOXAZIN when contained in water soluble bags individually packed in sealed sachets.

Schedule 7 – Amendment

FLUMIOXAZIN – Amend entry to read:

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

1.6 MAVACOXIB

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of mavacoxib and decided to seek advice from the ACCS on the following:

Mavacoxib – proposal to include mavacoxib in Schedule 4.

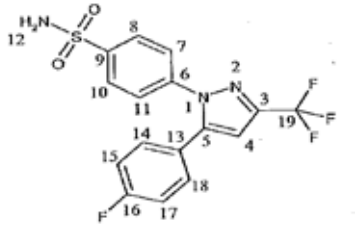
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 4 entry be created for mavacoxib. The Committee also recommended an implementation period of within six months after the delegate's final decision.

BACKGROUND

Mavacoxib belongs to the coxib class of non steroidal anti-inflammatory drugs (NSAIDs). The mechanism of action for mavacoxib is through the selective inhibition of the cyclooxygenase-2 enzyme (COX-2), which plays a major role in the synthesis of prostaglandins responsible for mediating the pain and inflammatory response in tissues and organs.

The IUPAC and CAS name of mavacoxib is 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide and the structure is:



Mavacoxib is closely related to the human drug celecoxib. Celecoxib is a NSAID used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain and painful menstruation. In August 1999, the NDPSC considered a Australian Drug Evaluation Committee's (replaced in 2010 by the Therapeutic Goods Administration's Advisory Committee on Prescription Medicines ACPM) recommendation for the registration of a human therapeutic containing celecoxib. The NDPSC noted that celecoxib was a new class of agent which inhibits COX-2 and decided that inclusion in Schedule 4 was appropriate.

The major effect of all NSAIDs is to decrease the synthesis of prostaglandins by reversibly inhibiting COX, an enzyme that catalyses the formation of prostaglandins and thromboxanes from the precursor, arachidonic acid. The result of NSAID-induced COX inhibition is decreased production of prostaglandins, which leads to decreased pain and inflammation. Prostaglandins are involved in maintaining gastrointestinal mucosal integrity as well as regulating renal blood flow and both acute and chronic toxicity often involves the gastrointestinal and renal systems. Two isoforms of COX have been identified. COX-1 has been proposed to generate prostaglandins that maintain organ function, protect the integrity of the gastric mucosa, and generate platelet-derived thromboxane responsible for platelet aggregation and vasoconstriction. COX-1 is expressed in all tissues, whereas COX-2 is induced during the inflammatory response and produces prostaglandins that mediate pain and inflammation. COX- 2 is also expressed in kidneys and vascular endothelium. Classic, older NSAIDs inhibit COX-1 more than COX-2, whereas the newer class of NSAIDs inhibit COX-2 predominantly, decreasing gastrointestinal adverse effects. However, selectivity of inhibition may be lost upon administration of large doses.

XXXXX has submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking the approval of a new active ingredient, mavacoxib and registration of XXXXX.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for mavacoxib. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Mavacoxib is not currently specifically scheduled. However, celecoxib is listed in Schedule 4 and would appear to capture mavacoxib as a derivative.

INITIAL SUBMISSIONS

Applicant's Submission

The XXXXX Risk Assessment Technical Report found that, based on the toxicity profile of mavacoxib and need for veterinary diagnosis of the indicated condition (osteoarthritis in dogs), mavacoxib XXXXX should be included in Schedule 4.

Other XXXXX conclusions included:

- There are no objections on human health grounds to the approval of mavacoxib TGAC XXXXX.
- As XXXXX products containing mavacoxib will not be used in food producing animals, no ADI or ARfD is required to be established at this time.
- No re-entry or re-handling statements are required.
- XXXXX.

Toxicology

Members noted the following toxicology summary for the TGAC mavacoxib:

XXXXX

- TGAC mavacoxib has low acute oral toxicity in XXXXX and dermal toxicity in XXXXX.
- Mavacoxib was not a skin irritant in XXXXX or skin sensitiser in XXXXX, but was found to be a slight eye irritant in XXXXX. No acute inhalational studies were submitted, however, the evaluator asserted that it was unlikely to be of significant inhalation toxicity.
- Mavacoxib was absorbed rapidly and almost completely in the gastrointestinal tract. It is distributed widely in the body and slowly excreted unchanged, principally in the faeces. The overall half life XXXXX. As a consequence, daily dosing in XXXXX resulted in the death of XXXXX from day XXXXX onwards at all doses. When treatment stopped on day XXXXX the deaths continued for a further two weeks, suggesting that mavacoxib had accumulated and continued to exert its toxic effects long after treatment ceased.
- No reproductive or developmental toxicity studies were submitted. However the applicant reported that inhibition of prostaglandin synthesis by NSAIDs may adversely affect pregnancy and/or embryo-foetal development. Data from epidemiological studies on humans suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy.
- Although mavacoxib is of low acute toxicity, its capacity for causing irreversible toxicity or neurotoxicity is unknown. The available toxicokinetic and toxicity data suggests that mavacoxib will be hazardous with repeated oral exposure.

Members noted the following toxicology summary for the formulated product.

- No acute toxicity studies for the product were submitted but an acute oral tolerance study was carried out in XXXXX. Single XXXXX oral doses were administered to XXXXX. The clinical effects observed were characteristic of NSAID toxicity. It was

possible that at high doses the selective COX inhibition was lost and as a consequence more severe gastrointestinal ulceration occurred.

- Mavacoxib in XXXXX was administered orally XXXXX. No critical effects observed. Reversible non-adverse elevated blood urea nitrogen levels were observed at all dose levels, which are associated with decreased urine flow for COX-inhibitors in XXXXX. A NOEL of XXXXX was established.
- XXXXX were not expected to adversely alter the toxicity profile established for TGAC mavacoxib. XXXXX. Thus, it was considered that the toxicity profile of the formulated product will be based on the toxicity of mavacoxib.

Use pattern / Exposure

- Members of the public, as XXXXX, may be exposed to the product when XXXXX administering it/them into XXXXX. There will be opportunity for dermal, oral and accidental ocular exposure.
- Consumption of a whole package XXXXX by a toddler as an acute accidental exposure event is possible. The consumption of XXXXX is equivalent to an exposure of XXXXX mavacoxib as a single acute event. For a 10 kg toddler this consumption as a single acute event represents an oral exposure of XXXXX.
- Repeated ingestion, especially within 30 d may be considered to be toxic or life threatening, since the toxicity of mavacoxib would be difficult to reverse given its very slow elimination.
- The main occupational use of the product will be by veterinarians, veterinary nurses, or animal managers. Workers may be exposed when XXXXX from a blister pack and administering into XXXXX. There will be opportunity for dermal, oral and accidental ocular exposure. While there are no surrogate exposure guides that may be used to estimate worker exposure levels, when the products are administered the exposure from these routes would be considered minimal and unlikely to result in exposure to a toxicologically significant dose.
- Post-application dermal, oral or ocular exposure to trace amounts of mavacoxib may continue if the user takes no steps to wash hands after administration. However these amounts are also unlikely to result in exposure at toxicologically significant dose levels.

Hazard classification - TGAC

Mavacoxib is not listed on the Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database. The evaluator recommended classification of mavacoxib as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances*, with the following risk phrases:

- R22 'Harmful if swallowed'
- R48/25 'Danger of serious damage to health by prolonged oral exposure'

In a one month repeat dose oral study in XXXXX, deaths and/or moribund requiring euthanasia were seen in XXXXX. Deaths were observed to such an extent that dosing was ceased on day XXXXX. The evaluator therefore indicated that the data supported the above phrases.

· R61 (Reproductive Category 2) 'May cause harm to the unborn child'

Although there was no reproductive toxicity data available, classification as a Category 2 reproductive toxicant for developmental toxicity was considered appropriate as mavacoxib is a COX-2 inhibitor belonging to NSAID class compounds. The epidemiology data also suggested that NSAIDs may adversely affect pregnancy and/or embryo/foetal development. Further the Therapeutic Goods Administration has classified NSAIDs as Pregnancy Category C compounds ("*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*".)

Members noted the following cut-off concentrations for the above hazard classification recommended by the evaluator:

Conc. ≥ 25%	R61; R22; R48/25
≥ 10% Conc. < 25%	R61; R48/25
≥ 1% Conc. < 10%	R61; R48/22
≥ 0.5% Conc. < 1%	R61

XXXXX

Applicant's Response to the Evaluation Report

The evaluator advised that XXXXX had considered XXXXX Report, including the scheduling recommendation, and indicated that there were no objections.

February 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that relevant matters under Section 52E (1) included (b) the purpose and extent of use; and (c) toxicity of a substance.

Members agreed that although mavacoxib was a slight eye irritant, it was neither a skin irritant nor a skin sensitiser and it had low acute oral and dermal toxicity. Members also noted that although it is a relatively new drug, mavacoxib had already been registered in the European Union.

A number of Members noted, however, that:

- The slow elimination of mavacoxib was a risk. Members agreed that this could be mitigated by the inclusion of adequate label warning statements and restricted supply as a Schedule 4 substance.
- Will be available in the form of XXXXX, therefore potentially attractive to children. A Member asserted that the proposed label warning statements were sufficient to minimise this risk.
- A few adverse toxic events, such as gastrointestinal ulceration, were reported in XXXXX. Members agreed, however, that while any potential human health risk of this type was diminished as there was little likelihood for human misuse, any scheduling entry should still pick up all uses of mavacoxib, not just animal use, to minimise unintended leakage for human therapeutic use.

Members agreed that the condition being managed was one requiring veterinary diagnosis. In addition, the prolonged half-life of mavacoxib meant that ongoing veterinary monitoring and involvement was required, particularly as there may be potential for interactions with other drugs. Members agreed that, together with being a relatively new drug, these issues justified Schedule 4 controls being applied to mavacoxib.

Members then considered the best way to effect these Schedule 4 controls. One Member noted that, as the closely related human drug celecoxib was currently in Schedule 4, there may not be a need to list mavacoxib in Schedule 4 separately. Other Members argued that, for clarity, mavacoxib needed a separate schedule entry.

Implementation date

Members agreed that six months would be sufficient time to implement the proposed change.

DELEGATE'S DISCUSSION

The delegate concluded that the recommendations of the ACCS were clear and appropriately supported. The delegate agreed with these recommendations. The delegate also agreed that an early implementation date was appropriate to facilitate completion of the registration process for this new veterinary medicine.

The delegate agreed that the relevant matters under section 52E (1) of the Act appear to include (b) the purpose and extent of use and (c) toxicity of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include mavacoxib in Schedule 4. The delegate also decided that an implementation date of 1 September 2011 was appropriate (i.e. three months after publication of the final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that mavacoxib be included in Schedule 4. The delegate also confirmed an implementation date of 1 September 2011.

Schedule 4 – New entry

MAVACOXIB.

1.7 METOFLUTHRIN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of metofluthrin and decided to seek advice from the ACCS on the following:

Metofluthrin – proposal to include metofluthrin in Schedule 6.

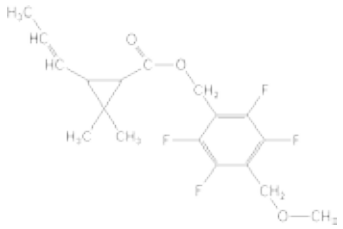
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 6 entry be created for metofluthrin. The Committee also recommended an implementation date of six months after the delegate's final decision.

BACKGROUND

Metofluthrin is a synthetic pyrethroid insecticide. This class of chemicals act on the nervous system of insects, disturbing the function of neurons by interacting with sodium channels. Other pyrethroid insecticides include transfluthrin, permethrin, deltamethrin, esfenvalerate and alpha-cypermethrin. While some of these share structural similarity with metofluthrin, this does not appear to be sufficient to class metofluthrin as a derivative (for the purpose of scheduling) of any of these compounds.

The IUPAC and CAS chemical name for metofluthrin is 2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl]benzyl (*EZ*)-(1*RS*)-*cis*-*trans*-2,2-dimethyl-3-prop-1-enylcyclopropanecarboxylate and the structure is:



XXXXX submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking the approval of a new technical grade active constituent (TGAC) metofluthrin.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for metofluthrin. The delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Metofluthrin is not currently scheduled.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX Report proposed that the mode of action for the observed liver tumours in XXXXX at doses equivalent to or exceeding the maximum tolerated dose were not relevant to humans, and that based on its toxicity profile of moderate acute inhalation toxicity and neurotoxicity XXXXX it was appropriate to include metofluthrin in Schedule 6.

Other XXXXX conclusions included:

- There were no objections on human health grounds to approval of metofluthrin.
- No ADI or ARfD were established for metofluthrin, as the active was not intended for direct use in food producing crops or in food producing animals.

Toxicology

Members noted the following toxicology summary for the TGAC metofluthrin:

XXXXX

- Metofluthrin had low acute toxicity via oral XXXXX and dermal XXXXX routes and moderate toxicity via the inhalational route. XXXXX. Members noted that the moderate inhalational LC_{50} was consistent with the acute inhalation factor in the Scheduling Policy Framework for Schedule 6.

- Metofluthrin was a slight skin irritant in XXXXX, but was not an eye irritant XXXXX. XXXXX was negative for skin sensitisation.
- Metofluthrin was readily absorbed through the gastrointestinal tract of XXXXX and rapidly excreted in the faeces and urine. The highest tissue levels of metofluthrin were found in the liver following single and repeat-dose administration. Absorbed metofluthrin was nearly completely metabolised. There were no metabolites identified in the metabolism studies as being toxicologically significant. In a percutaneous study in XXXXX, dermal absorption of metofluthrin after dermal administration was XXXXX.
- In a XXXXX repeated inhalation toxicity study, XXXXX were exposed to the mist aerosol at doses of XXXXX. XXXXX died following exposure at XXXXX. Necropsy was performed on all animals that died, and a number of findings were observed, however the cause of death could not be absolutely determined. There was an increased incidence of tail tremor and tremor observed during exposure at XXXXX. Immediately following exposure at XXXXX, tremor, hypersensitivity, ataxic gait, tiptoe gait, convulsion, hypothermia and lateral position were observed in XXXXX. There was a significant but transient reduction in food and water consumption in males at XXXXX. These changes may be related to nervous signs as they were only noted at the beginning of exposure. There were no treatment-related changes in bodyweight, urinalysis, ophthalmology, haematology or blood biochemistry. XXXXX.
- In a XXXXX oral toxicity study in XXXXX was found dead on day XXXXX of treatment at XXXXX. Prior to death, tremor was observed in this animal and gross pathology showed dark changes and enlargement of the liver. Tremor was observed during days XXXXX, but disappeared by XXXXX. A significant reduction in bodyweight and bodyweight gain was observed in XXXXX, while food consumption was significantly reduced in XXXXX. These changes were transient, appearing only in the early phase of the treatment period and could be considered to result from palatability of the test substance. There was a significant increase in the absolute liver weight in XXXXX, and relative liver weight at XXXXX. Liver effects observed during gross pathology and histopathology included dark changes in the liver of XXXXX, hepatocellular hypertrophy in XXXXX, a decrease of slight or mild diffuse hepatocyte vacuolation in both sexes at XXXXX, and an increased number of smooth endoplasmic reticulum in XXXXX (a Member noted that this would need to be confirmed through electron microscopy examination). These changes were not observed at the end of the recovery period. XXXXX.
- In repeat-dose neurotoxicity studies, clinical signs of toxicity observed in XXXXX included tremor and vomiting XXXXX. In XXXXX, tremor was noted at XXXXX, while vomiting was observed at doses of XXXXX. In XXXXX, tremor was observed in maternal animals at XXXXX in a developmental study. Vocalization and hyperactivity were also noted in a XXXXX dermal study in XXXXX. Clinical signs appeared within XXXXX of dosing and had generally disappeared by XXXXX.

Neurological signs were more pronounced in XXXXX via the inhalation route XXXXX, with clinical signs reported at XXXXX.

Use Pattern / Exposure

- The primary use of metofluthrin would be in XXXXX. It was to be used as XXXXX. There were no proposed agricultural uses for metofluthrin. The applicant had not submitted an application for registration of a product containing metofluthrin.

Hazard Classification

- Metofluthrin is not listed on Safe Work Australia's Hazardous Substances Information System Database.
- The evaluator recommended that metofluthrin be classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances*, with the risk phrase of R20 "*Harmful by inhalation*".
- Additionally the evaluator indicated that the safety phrase "*Avoid contact with skin*" should be applied for pyrethroid pesticides which may cause paresthesia. For metofluthrin this should apply at concentrations of 25 per cent or more.
- The current GHS classification for metofluthrin would therefore be:

NOHSC Classification	GHS Classification	Hazard Communication
Xn; R20 Harmful by inhalation	Acute inhalation toxicity Category 4	Warning  Harmful if inhaled

Applicant's Response to the Evaluation Report

The evaluator advised that XXXXX had considered the XXXXX Report, including the scheduling recommendation, and advised that there were no objections.

February 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

The relevant matters under section 52E (1) of the Act appear to include (a) risks and benefits of the substance and (c) toxicity.

Members noted that metofluthrin had low acute oral and dermal toxicity and slight eye irritancy. Members also noted that, in addition to metofluthrin having low dermal toxicity, it was not intended to be applied on the skin and that dermal exposure was likely

to be insignificant. In addition, a Member noted that the liver effects were likely a result of the compound promoting enzyme activity, and this would explain why tolerance occurred. As such, these effects were unlikely to be a major concern. It was also noted that the neurotoxicity results were in line with expectations for this class of compounds.

However, it was noted that the major route of exposure was via inhalation and that, in addition to the moderate acute inhalation toxicity finding, some results of the inhalation study raised particular concern (in one study all the exposed animals died at XXXXX). A Member asserted that as metofluthrin would be used as an insect repellent in domestic situations this would lead to repeated exposures to metofluthrin via inhalation. Members agreed that a Schedule 6 listing was appropriate.

Members also agreed that there was insufficient information to establish a low concentration cut-off from Schedule 6.

Implementation date

Members agreed that six months would be sufficient time to implement the proposed change.

DELEGATE'S DISCUSSION

The delegate concluded that the recommendations of the ACCS were clear and appropriately supported. The delegate agreed with these recommendations. The delegate also agreed that an implementation period of six months was appropriate.

The delegate agreed that the relevant matters under section 52E (1) of the Act included (a) risks and benefits of the substance; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate decided to include metofluthrin in Schedule 6. The delegate also decided that an implementation date of 1 January 2012 was appropriate (i.e. six months after publication of the final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that metofluthrin be included in Schedule 6. The delegate also confirmed an implementation date of 1 January 2012.

Schedule 6 – New entry

METOFLUTHRIN.

1.8 PROQUINAZID

DELEGATE'S PROPOSAL

The delegate considered the scheduling of proquinazid and decided to seek advice from ACCS on the following:

Proquinazid – proposal to include proquinazid in Schedule 6 or 7.

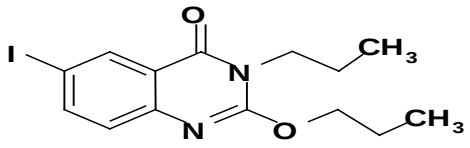
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 6 entry be created for proquinazid. The Committee also recommended an implementation date of no more than 6 months after the delegate's final decision.

BACKGROUND

Proquinazid belongs to the quinazolione group of fungicides. Proquinazid blocks the development of appressorial germ tube in powdery mildew, thus preventing the spores from germinating. In the presence of proquinazid, the spores would produce a germ tube which will elongate without forming an appressorium (infection peg) from which infection of cells can proceed. In the absence of an appressorium, the spores cannot attach themselves into the plant within 24 h. Consequently, the spores run out of energy and die.

The CAS name of proquinazid is 6-iodo-2-propoxy-3-propyl-4(3H)-quinazolinone and the structure is:



XXXXX submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking the approval of a new active ingredient, proquinazid, and XXXXX.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for proquinazid. A delegate agreed that this was a matter for scheduling consideration and that advice from the ACCS was needed. The delegate noted that the XXXXX scheduling recommendation was largely based on assessment of the carcinogenicity risk. It was noted that this end point can be difficult to assess for scheduling. Therefore, for the purposes of public consultation and seeking advice from ACCS the delegate's proposal indicated consideration of a Schedule 6 or Schedule 7 entry.

SCHEDULING STATUS

Proquinazid is not currently scheduled.

INITIAL SUBMISSIONS

Applicant's Submission

The XXXXX Report concluded that, based on the toxicity profile and limited evidence of carcinogenic effects, proquinazid should be included in Schedule 6 with no cut-off rather than Schedule 7.

Other XXXXX conclusions included:

- There were no objections on human health grounds to the approval of the new active ingredient, proquinazid, or XXXXX.
- The Acceptable Daily Intake (ADI) was established at 0.01mg/kg bw/d based on a NOAEL of 1.2 mg/kg bw/d in a XXXXX study and applying the default 100-fold safety factor to account for potential inter- and intra-species differences.
- The Acute Reference Dose (ARfD) was established at 0.2 mg/kg bw/d based on a LOAEL of 19 mg/kg bw/d in a XXXXX and using the default 100-fold safety factor to account for potential inter- and intra-species differences, which is considered sufficient for the minor and largely transient effects seen.

XXXXX

The evaluator advised that the toxicology assessment summary of proquinazid was taken from the results of experiments conducted by the European Union (EU). Raw data were also provided to XXXXX for all studies in the EU report. The evaluator indicated that the EU report contained thoroughly evaluated studies and was well presented. The toxicology studies were conducted in accordance with contemporary test guidelines.

Australian toxicological assessments have generally used the terms No Observed Effect Level (NOEL) and Lowest Observed Effect Level (LOEL) instead of No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) (the EU approach to human health assessment). However, as XXXXX report relied heavily on the international assessment report by the EU, the evaluator adopted the NOAEL and LOAEL approach using scientific justification for their adoption.

Toxicology

Members noted the following toxicology summary for the technical grade active proquinazid:

XXXXX

- Proquinazid had low acute oral XXXXX, dermal XXXXX and inhalational XXXXX toxicity in XXXXX. It was a slight skin and eye irritant in XXXXX. Skin sensitization testing in XXXXX did not demonstrate a potential for skin sensitization.

- In a XXXXX carcinogenic study, proquinazid XXXXX was administered to XXXXX. The NOAEL was XXXXX based on test substance related increases in non-neoplastic liver lesions and changes in thyroid hormones and pathology at XXXXX, discoloured teeth in XXXXX was also considered to be an adverse effect. Proquinazid was oncogenic, causing benign hepatocellular adenomas XXXXX and thyroid follicular cell tumours in XXXXX. Decreased body weight and body weight gain occurred in XXXXX. An increased incidence of hepatocellular adenomas were observed in XXXXX, but not in XXXXX. At XXXXX, the incidence of hepatocellular adenomas in XXXXX was XXXXX. In XXXXX there was also an increased incidence of intestinal-type 'cholangiocarcinomas' but it was uncertain if this lesion should be regarded as a tumour.
- The evaluator asserted that the observed increased incidence of hepatocellular adenoma was likely to be as the results of poor dose-selection, as there is evidence to indicate that these XXXXX doses were excessive and had exceeded the maximum tolerated dose (MTD) for a carcinogenicity study. Evidence that the MTD had been exceeded was a marked reduction in bodyweight gain (greater than 10 per cent) and significant liver toxicity (altered liver enzymes, increased liver weight, degenerative hepatocytes). At XXXXX, bodyweight gains were reduced by XXXXX. The observed hepatocellular adenomas are likely a secondary consequence of overt liver toxicity due to excessively high dose levels, and not robust evidence alone of a carcinogenic potential for proquinazid.
- With regard to carcinogenic concerns, the evaluator also asserted that:
  - as no metatases were detected in distant organs, the intestinal-type cholangiocarcinomas seen in XXXXX only should not be regarded as malignant tumours;
  - the benign hepatocellular adenomas seen only in XXXXX (a slight increase considered 'equivocal' in XXXXX in the presence of peroxisome proliferation) were not considered to provide robust evidence that proquinazid be considered a presumed human carcinogen;
  - intestinal-type cholangiocarcinomas and hepatocellular adenomas lesions were only seen at doses that exceeded the maximum tolerated dose and were most likely a secondary consequence of prolonged and severe hepatic toxicity;
  - proquinazid did not exhibit a mutagenic or genotoxic potential in vitro, or a genotoxic potential in vivo, and there was a clear threshold level under which these lesions did not occur; and
  - the increased incidence of benign thyroid follicular cell tumours seen in XXXXX (a slight increase considered 'equivocal' in XXXXX) were considered to be XXXXX and not relevant to humans.

Members noted the following toxicology summary for the product:

XXXXX

- The product was of low acute toxicity by the oral XXXXX and dermal XXXXX routes in XXXXX. The formulation was a severe eye and skin irritant in XXXXX but was not a skin sensitiser in XXXXX. Members noted that the acute toxicity appeared to arise from product formulation, e.g. solvents / excipients, not toxicity of the active constituent proquinazid. Members agreed that this was not a scheduling concern; specific formulation concerns were an issue for the regulator as part of any product approval separate to scheduling.
- No acute inhalation toxicity studies were submitted for the product and there was insufficient information to allow for the determination of the LC_{50}, though it was considered that the product would have low acute inhalation toxicity. The evaluator asserted that as the product causes severe skin and eye irritation XXXXX it was expected to be a respiratory irritant.

Use Pattern / Exposure

Members also noted the following summary of use pattern and exposure information from the XXXXX report:

- This product was not intended for domestic use.
- XXXXX. Workers may be exposed to the product when opening containers, mixing/loading, during application and cleaning up spills and equipment. The main route of exposure to the product/spray will be dermal and inhalational, although ocular exposure is also possible.
- The principal hazards will arise from irritation of the nose, throat, skin and eyes if accidental contact is made when opening the containers and preparing the spray mix. However, as the product is diluted at the maximal rate of XXXXX is unlikely to be an irritant. XXXXX:

XXXXX

- Bystander exposure may occur if members of the public walk past an area at the time of treatment with the product or during re-entry. Bystander exposure was likely to be lower and less frequent than that of workers using the product.

Hazard Classification - TGAC

- Proquinazid is not listed on Safe Work Australia's Hazardous Substances Information System (HSIS) Database. XXXXX has determined that proquinazid should be classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances*, with the following risk phrases: R40 (Carc. Cat 3) "*Limited evidence of carcinogenic effect*". This phrase was to apply to concentrations of 1 per cent or more.

XXXXX

Applicant's Response to the Evaluation Report

The evaluator advised that XXXXX had considered the XXXXX Report, including the scheduling recommendation (Schedule 6 with no cut-offs), and accepted this proposal for scheduling.

February 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

COMMITTEE DISCUSSION

The Committee generally agreed that the relevant matters under section 52E (1) of the Act included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

Members noted proquinazid's toxicity profile, especially its questionable carcinogencity potential and low acute toxicity, and debated whether it warranted control as a Schedule 5, Schedule 6 or Schedule 7 poison. Although proquinazid had low acute oral, dermal and inhalational toxicity, Members agreed that a Schedule 5 classification was inappropriate because of the carcinogenic findings, particularly with two species showing effects. Members then debated whether this concern could best be addressed by including proquinazid in Schedule 6 or in Schedule 7.

Several Members noted that the methodology used in some of the experiments (i.e. animals exposed to excessive concentrations), was questionable as there comes a point where carcinogenic effects may be the result of stress on the animal from the effects of excessive concentrations.

A Member noted that the intestinal carcinoma cholangiocarcinoma was XXXXX specific and not indicative of a carcinogenic risk for humans. The Member further indicated that lesions observed in the experiments were not neoplastic. Members also noted a recent UK Committees' (The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment, and The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment) communication indicated uncertainty that the lesions termed cholangiocarcinomas were truly neoplastic. The above Committees also noted that the pathology seen with proquinazid lacked the expected characteristics of those caused by a genotoxic carcinogen.

The Committee generally agreed that the data indicated that proquinazid was not a potent carcinogen. Members also noted, however, that this still raised some concern regarding relevance to humans which could not entirely be discounted. Members generally agreed therefore that proquinazid should not be listed in Schedule 7. Instead, the risks arising from its use could be adequately managed by listing it in Schedule 6.

As a separate matter, a Member indicated that although proquinazid was not intended for domestic use, the proposed pack size, XXXXX, might promote leakage into the hobby

farm market. Members agreed, however, that this was a matter best addressed by the APVMA.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACCS were clear and appropriately supported. The delegate also agreed that an early implementation date was appropriate.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate decided to include proquinazid in Schedule 6. The delegate also decided that an implementation date of 1 September 2011 was appropriate (i.e. three months after publication of the final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that proquinazid be included in Schedule 6. The delegate also confirmed an implementation date of 1 September 2011.

Schedule 6 – New entry

PROQUINAZID.

2. MATTERS INITIALLY REFERRED TO ACMS#2 – FEBRUARY 2011

2.1. PROPOSED CHANGES TO PART 4 OF THE SUSMP (THE SCHEDULES)

2.1.1 CHLORAMPHENICOL

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of chloramphenicol and decided to seek advice from the ACMS on the following:

Chloramphenicol – consideration of amending the Schedule 3 entry to restrict chloramphenicol for ophthalmic use only in the treatment of bacterial conjunctivitis.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current scheduling of chloramphenicol remained appropriate.

BACKGROUND

Chloramphenicol is a bacteriostatic antibiotic with a broad spectrum of action against both Gram-positive and Gram-negative bacteria. It prevents bacterial reproduction by selectively inhibiting protein synthesis by bacterial ribosomes with a reported efficacy of 91 per cent to 93 per cent in ocular infections, and is active against up to 94 per cent of ocular pathogens.

Chloramphenicol is extensively used in the topical treatment of ear and, in particular, eye infections. Infections due to *Salmonella typhi, Haemophilus influenzae* and *Bacteroides fragilis* have previously been the principal indications for chloramphenicol use. It is also used topically in the treatment of skin infections. Acquired resistance has been reported.

In February 2009, the NDPSC noted that the November 2008 meeting of New Zealand's (NZ) Medicines Classification Committee (MCC) was considering reclassification of chloramphenicol eye preparations from prescription medicine to restricted medicine. Main matters discussed were the possible development of bacterial resistance to chloramphenicol and 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 additional supporting information was provided. Information was subsequently submitted to the May 2009 MCC meeting, which agreed to reclassify chloramphenicol eye preparations from prescription medicine (except when sold in practice by a registered optometrist) to restricted medicine (except when sold in practice by a registered optometrist).

In October 2009, the NDPSC decided to harmonise with NZ by including chloramphenicol for ophthalmic use in Schedule 3. Members generally agreed that there appeared to be little, if any, significant difference between the ability of GPs and pharmacists in providing differential diagnosis between mild cases of bacterial or eye infection.

In February 2010, the NDPSC considered post-meeting public submissions on the above decision. Several Members asserted that these submissions only reiterated arguments already considered at the October 2009 meeting. Members confirmed the October 2009 decision to include chloramphenicol for ophthalmic use in Schedule 3.

SCHEDULING STATUS

Chloramphenicol is currently listed in Schedule 3 for ophthalmic use only, and is listed in Schedule 4 for all other uses. This is essentially harmonised with NZ.

INITIAL SUBMISSIONS

Applicant's Submission

The TGA's Advisory Committee on Non-prescription Medicines (ACNM) requested a narrowing of the October 2009 NDPSC decision by restricting the use of chloramphenicol in Schedule 3 to ophthalmic use when for the treatment of bacterial conjunctivitis only.

The ACNM request followed the evaluation of a submission to vary the registration of a chloramphenicol eye drop 5 mg/mL and eye ointment 10 mg/g. At its August 2010 meeting, the TGA's ACNM decided to grant approval of these products, subject to an agreement from the sponsor to amend the labels, Product Information (PI) and Consumer Medicine Information (CMI).

The ACNM's recommendations are summarised as follows:

- Stated that the ophthalmic use of chloramphenicol for the treatment of bacterial conjunctivitis was the only indication appropriate for diagnosis by a pharmacist. Contended that most other eye infections required medical diagnosis and that some other eye infections might have potentially serious consequences (including blindness) if not correctly diagnosed.
- The ACNM evaluator suggested that the current reference to "other common eye infections" in the label indications might be assumed to include viral conjunctivitis, and noted that current clinical guidelines did not routinely recommend ophthalmic use of chloramphenicol to treat common eye infections seen in pharmacies, such as blepharitis, hordeolum (stye) and chalazion.
- Argued that the October 2009 rescheduling decision had followed the reclassification of ophthalmic chloramphenicol to OTC by the UK Medicines and Healthcare

products Regulatory Agency (MHRA), which had restricted its use to the treatment of acute bacterial conjunctivitis in adults and children aged two years and over, for a maximum of five days.

- Noted that the NDPSC did not restrict the Schedule 3 chloramphenicol entry to any specific indications. Contended that the label indications for chloramphenicol 5 mg/mL eye drops and 10 mg/g eye ointment supplied as Schedule 3 products should be only "Topical antibiotic preparation for the treatment of bacterial conjunctivitis".
- Emphasised that the Pharmaceutical Society of Australia (PSA) protocol for OTC supply of ophthalmic chloramphenicol advised its use only for acute bacterial conjunctivitis. The PSA protocol was based on a practice guidance developed by the Royal Pharmaceutical Society of Great Britain (RPSGB) in the UK for OTC supply of ophthalmic chloramphenicol.
- Stated that pending recommendation from the ACMS regarding an appropriate Schedule 3 entry for chloramphenicol, the ARTG indications could remain unchanged, ie. "For the treatment of bacterial conjunctivitis and other superficial ocular infections caused by chloramphenicol-sensitive organisms". ACNM Members did note that it was not necessary for scheduling to be limited in line with the ARTG.

Members also noted a number of additional ACNM additional comments as follows:

Labelling

- Bacterial conjunctivitis was the only indication appropriate for diagnosis by a pharmacist, and the PSA protocol for OTC supply of ophthalmic chloramphenicol only advises its use for acute bacterial conjunctivitis.
- To revise the indications in the PI to "For the treatment of bacterial conjunctivitis. For use under medical supervision only in the treatment of other superficial ocular infections caused by chloramphenicol-sensitive organisms", to capture both the appropriate OTC indication and other uses which should be under medical supervision.
- To amend the CMI to include additional information describing bacterial conjunctivitis and its symptoms.
- The directions for use on the labels, PI and CMI should clearly state that these products should not be used on children < 2 years of age except on medical advice.

Treatment and appropriate age groups

- Advised that in the UK, the MHRA did not allow the use of OTC ophthalmic chloramphenicol in children < 2 years. This was intended to avoid the risk of the 'grey baby syndrome', a type of circulatory collapse due to high levels of chloramphenicol caused by the inability of infants to conjugate chloramphenicol or excrete the unconjugated drug.

- Highlighted that in Australia, there is no age restriction on the use of ophthalmic chloramphenicol as prescription products.
- The ACNM evaluator also recommended that these products should not be used in children < 2 years of age, except on medical advice, to avoid the risk of grey baby syndrome, and to exclude serious causes of a red eye that can lead to permanent impairment of vision without ocular examination, particularly when the eyes of infants are developing.

Duration of treatment

- Advised that the sponsor's originally proposed eye drops label XXXXX was inconsistent with the duration in the PI (continue treatment for at least 48 hours after the eye appears normal). In addition, the eye ointment labels did not include any treatment duration.
- The UK MHRA limited treatment with OTC ophthalmic chloramphenicol to five days, to ensure that unsupervised use did not contribute to an increase in resistance.

XXXXX.

Pre-meeting Submissions

Two submissions were lodged. XXXXX did not object to the proposal to amend the Schedule 3 entry for chloramphenicol to restrict use to the treatment of bacterial conjunctivitis. Reiterated that the PSA document issued in May 2010, 'Provision of chloramphenicol for ophthalmic use as a Pharmacist Only Medicine', provided guidance to pharmacists on the appropriate use of chloramphenicol in bacterial conjunctivitis, including how to differentiate it from viral conjunctivitis and allergic conjunctivitis.

XXXXX did not support further restricting chloramphenicol Schedule 3 entry to the treatment of bacterial conjunctivitis. The following comments were made:

- Questioned the reasoning for this further restriction, particularly whether there was evidence of public safety issues arising from the current, less restrictive Schedule 3 listing for chloramphenicol.
- Argued that the consequences of chloramphenicol restriction from 'ophthalmic use only' to 'the treatment of bacterial conjunctivitis' would be:
  - A more restrictive listing could not be recommended by pharmacists for the treatment of non-complex eye conditions such as blepharitis or styes, even though this would be consistent with the products' registered indications.
  - If this greater restriction was implemented and pharmacists should inadvertently recommend chloramphenicol products for other eye infections for which the product was indicated, they would be breaching the law.

- Contended that topical [ocular] chloramphenicol was generally well tolerated, and adverse effects such as hypersensitivity, burning, and stinging sensations were uncommon.
- Patients have quicker and easier access to effective treatment for the treatment of minor bacterial eye infections.
- Pharmacists currently triaged patients with conjunctivitis on a regular basis to determine the appropriate course of action. In case of complications or concerns, pharmacists referred patients to the GP.
- Chloramphenicol was the gold standard (eye drops) and would be effective against nearly all cases of acute bacterial conjunctivitis in adults and children who presented in the pharmacy.
- Mentioned the PSA protocol had been developed for use by pharmacists.

May MCC and October NDPSC 2009 meetings

Members noted the following from the NZ May 2009 MCC meeting:

- 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 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 have some experience with diagnosing and treating conjunctivitis.
- 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.

Members noted the following discussions from the October 2009 NDPSC meeting:

- A Member noted that the down scheduling was a significant change that involved the availability of an appropriate protocol for chloramphenicol to provide training to pharmacists. The Member suggested that it may therefore be more appropriate to wait for a full application to drive this consideration rather than rely on referral from

the NZ MCC. Members noted that it was not the role of the NDPSC to approve professional protocols.

- Several Members noted that the key factor in considering the down scheduling proposal was the relative abilities of the pharmacist *vs*. GP 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 diagnosis than a pharmacist.
- One Member argued that perhaps an optometrist would be better placed 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 allow a relatively well qualified health professional to supply a substance with which they have had substantial experience. The NDPSC 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 NDPSC's attention to the consequences of patients who might not be correctly diagnosed or not referred to a GP when they should have been, with the most serious consequence being blindness. Several other Members contended, however, that while misdiagnosis might 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 have 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 to a GP, noting that pharmacists were already diagnosing patients and providing treatments with far less effective products.
- A Member noted that, if the NDPSC could satisfy itself that the benefits out-weighed 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.

February 2010 NDPSC meeting

The NDPSC considered post-meeting submissions and asserted that these reiterated arguments already considered at the October 2009 meeting rather than raising any substantially new concerns or issues. In particular, the post-meeting submissions:

- 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 viral 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.

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

EXPERT ADVISORY COMMITTEE DISCUSSION

Members discussed the potential benefits of restricting the current wording of chloramphenicol in Schedule 3 from ophthalmic use generally to bacterial conjunctivitis. A Member queried whether an alignment of chloramphenicol wording with its current indication would bring additional benefit to the public. A Member noted that the reason of the proposed rewording of chloramphenicol scheduling was to prevent the supply of chloramphenicol for purposes other than bacterial conjunctivitis. Another Member contended that inclusion of the indication in the schedule entry would not necessarily prevent the use of chloramphenicol outside of its indication. Another Member also stated that although limiting the scheduling wording for chloramphenicol to acute bacterial conjunctivitis may appear to assist regulators, it would be difficult to enforce in practice.

The Member also noted the role played by pharmacist professional practice standards in regulating how products are provided to the public and stated that these help to ensure the appropriate use of chloramphenicol. A Member noted that the indication for Schedule 3 chloramphenicol was listed in the ARTG, which could assist appropriate use of these products. Another Member also commented that since the October 2009 rescheduling decision, a protocol for the OTC supply of ophthalmic chloramphenicol had been developed and was available to assist pharmacists' professional judgement on the appropriateness of supplying chloramphenicol to patients.

Members noted that the current wording of the Schedule 3 chloramphenicol entry was consistent with the entries of other Schedule 3 substances with similar use patterns (e.g. sulfacetamide). A Member asserted, however, that a substance is usually included in Schedule 3 to reduce the need for the public to consult with a general practitioner. By including indication restrictions in the Schedule 3 entry, patients may assume that the specific indication was less serious and that general practitioner advice was not required. The Member contended that this assumption could result in an increase in pressure on pharmacists from the general public. Another Member noted that the inclusion of an indication in the schedule entry was usually reserved for cases where it was necessary to exclude an inappropriate indication and asserted that this was not the case for chloramphenicol.

Members discussed the purpose for which ophthalmic chloramphenicol was to be used. Members noted concerns regarding the potential for bacterial resistance associated with the use of chloramphenicol, however it was asserted that this risk was sufficiently mitigated by the Schedule 3 listing. Members also noted concerns regarding the efficacy

of chloramphenicol in the resolution of symptoms of acute bacterial conjunctivitis compared to other available treatments (i.e. saline solutions). A Member asserted that these matters were addressed by TGA registration processes and the use of chloramphenicol in the treatment of bacterial conjunctivitis was well established internationally.

Members also discussed the international scheduling status of chloramphenicol. A Member noted that in the UK since the reclassification of chloramphenicol for use in bacterial conjunctivitis from Prescription Only to Pharmacist Only, the sales of chloramphenicol had increased 50 per cent. The Members also noted that unlike Australia and NZ, in the UK use of ophthalmic preparations of chloramphenicol was restricted to children above 2 years of age. A Member raised concerns whether, similar to NZ, Schedule 3 medicines could be obtained without appropriate advice from a pharmacist (i.e. sold through online pharmacies). However, existing drugs and poisons legislation in Australia could preclude this from occurring. Members agreed that the risks associated with inappropriate use of chloramphenicol required mitigation.

Regulatory options other than scheduling were discussed. A Member queried whether more restrictive wording could be included in the CMI specifying the treatment of bacterial conjunctivitis only. The Member asserted that this option would address the concerns regarding inappropriate use of chloramphenicol and could preclude the need to amend the chloramphenicol entry. Other Members agreed that this approach (including appropriate labelling) would assist in ensuring appropriate chloramphenicol use by patients.

Members generally agreed that a more restricted wording of the Schedule 3 chloramphenicol entry would not result in further benefits concerning its ophthalmic use and agreed to recommend to the delegate that the current wording chloramphenicol remained appropriate.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (b) purposes for which a substance is to be used.

DELEGATE'S INTERIM DECISION

The delegate decided that the current scheduling of chloramphenicol remained appropriate.

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that the current scheduling of chloramphenicol remained appropriate.

2.1.2 FEXOFENADINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of fexofenadine and decided to seek advice from the ACMS on the following:

Fexofenadine – proposal to amend the current Schedule 2 fexofenadine entry to exempt oral fexofenadine for the short-term symptomatic relief of seasonal allergic rhinitis from the requirements of scheduling.

This consideration may include limiting the exemption to:

- small pack sizes (10 dosage units or less);
- packs containing not more than 5 days supply at the maximum dose recommended on the label;
- for the treatment of adults and children aged 12 years of age and over; and
- a maximum daily dose of 120 mg.

Consideration may also include whether the exemption from scheduling should be limited to products labelled to the effect of "*This product should not be used when pregnant or when breastfeeding except when advised by your Doctor or Pharmacist. Do not use with other antihistamines.*"

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that fexofenadine be exempt from scheduling when for the short-term symptomatic relief of seasonal allergic rhinitis (SAR) in adults and children 12 years of age and over when sold in small packs of 10 dosage units or less (i.e. not more than 5 days supply at the current maximum recommended dose) with a maximum daily dose of 120 mg.

The Committee recommended an implementation date of 1 September 2011 (three months following publication of the delegate's final decision).

The Committee further recommended that the delegate consider referral to the appropriate areas of the TGA regarding inclusion of a labelling warning statement requirement in the *Required Advisory Statements for Medicine Labels* for exempt preparations of fexofenadine to the following effect:
"This product should not be used when pregnant or when breastfeeding except when advised by your Doctor or Pharmacist. Do not use with other antihistamines."

BACKGROUND

Fexofenadine is an orally active non-sedating histamine H1-receptor antagonist used in the symptomatic relief of allergic conditions including SAR and chronic urticaria. Fexofenadine is the carboxylic acid metabolite of terfenadine.

In May and August 1996, the NDPSC 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 in November 1996, where the NDPSC noted additional safety data and decided that oral divided preparations of fexofenadine should be included in Schedule 3.

In February 1997, the NDPSC 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 NDPSC 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 NDPSC agreed that the decision to include fexofenadine as Schedule 3 remained appropriate.

In August 1998, the NDPSC agreed to include fexofenadine in Appendix H.

In November 1998 and February 1999, following recommendations from the Trans-Tasman Harmonisation Working Party, the NDPSC agreed to reschedule fexofenadine from Schedule 3 to Schedule 2. The New Zealand and Australian entries for fexofenadine were then harmonised in November 1999.

In October 2009, the NDPSC considered a request to exempt oral fexofenadine from scheduling for the short term treatment of SAR, deferred from the June 2009 meeting. The NDPSC decided that the current scheduling of oral fexofenadine (Schedule 2) remained appropriate. In February 2010, the NDPSC considered the same request referred from the NZ Medicine Classification Committee (MCC) along with pre-meeting submissions and again decided that the current scheduling of fexofenadine remained appropriate. The NDPSC's discussion at the October 2009 and February 2010 meetings are summarised below, under the Submissions heading.

SCHEDULING STATUS

Fexofenadine is currently listed in Schedule 2 in preparations for oral use. All other preparations are captured in Schedule 4.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX sought an exemption from scheduling requirements for oral fexofenadine (maximum 10 dosage units) when used for the short-term symptomatic relief (maximum 5 days of therapy) of SAR in adults and children 12 years and over, with a maximum daily dose of 120 mg.

The applicant also suggested the following wording for a new Appendix F warning entry to be associated with the exemption of fexofenadine: "*This product should not be used when pregnant or when breastfeeding except when advised by your Doctor or Pharmacist. Do not use with other antihistamines.*" Members noted that requirements for medicine labels are regulated by the TGA's *Required Advisory Statements for Medicine Labels* (RASML). Members further noted that Appendix F imposes controls on warning statements and general safety directions for scheduled substances other than medicines for human use which are compliant with the requirements of RASML - i.e. Appendix F does not apply to a substance exempted from scheduling. Fexofenadine was not listed in Appendix F, and there were currently no RASML requirements associated with fexofenadine.

The application noted the issues raised in the discussion at the October 2009 and February 2010 NDPSC meetings, namely concerns surrounding the use of fexofenadine in pregnancy, potential for misdiagnosis of SAR and a lack of data to support benefit over these risks. The application reiterated statements previously provided to the October 2009 meeting to address matters under s52E of the Act and also included new information to address these specific concerns. The main points of the application have been summarised below:

- Noted that fexofenadine is a Category B2 medicine:

  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 malformations or other direct of indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

- Proposed new labelling to address concerns over use in pregnancy. Asserted that these labels clearly communicate that the product should not be used by pregnant or breastfeeding women.

- Noted new epidemiological data indicating that the risk to the foetus of using fexofenadine during pregnancy may be lower than the current pregnancy categorisation suggests. Also noted data quantifying the secretion of fexofenadine into breastmilk suggesting that no clinically significant quantities could be measured in the breastfed infant.
- Stated that several products were currently available through grocery outlets despite a B1, B2, C or D pregnancy category and/or restriction on use during breastfeeding. Asserted that these products managed the risk of use in pregnancy and breastfeeding via warnings included on labelling.
- Asserted that exempt phenylephrine and phenylephrine/paracetamol combinations indicated for the treatment of runny/blocked nose (symptoms common to SAR) had the same pregnancy categorisation and very similar breastfeeding status to fexofenadine. Stated that as pregnant women were known to experience hormone-related sinusitis in pregnancy, the exemption from scheduling of these combinations was a reasonable surrogate safety test for fexofenadine being exempted from scheduling.
- Stated that in relation to misdiagnosis, the most likely outcome was a lack of symptom relief leading to discontinuation of therapy and the patient seeking professional advice. Asserted that this would be unlikely to impact the progression of diseases such as nasal polyps, nasal tumours or chronic sinusitis. Stated that the development and diagnosis of some of these conditions could take months/years and a 5 day delay in consulting a healthcare professional was not expected to result in any clinically significant events.
- Stated that the revised Consumer Medicine Information (CMI) leaflet included a section which specified symptoms usually not associated with hayfever (but possibly associated with infectious rhinitis, chronic sinusitis, nasal polyps or nasal tumours) to aid self-diagnosis.
- Asserted that the key to safe and efficacious use of unscheduled medicines was labelling addressing the known areas of potential concern. Noted that the NZ MCC raised similar concerns over the safety of fexofenadine, but decided that these could be addressed through labelling.
- Stated that an exemption for fexofenadine would facilitate access out-of-hours and noted that a 2009 survey showed that 33 per cent of patients were not able to purchase medication whilst suffering from SAR on at least one occasion due to pharmacy opening hours. Noted that 81 per cent of hayfever patients who treat their condition indicated that they would find it useful to be able to purchase hayfever medication outside of normal trading hours of pharmacy.
- Noted a survey showing that 4 per cent of pharmacies reported operating hours of 24 hours / 7 days a week, indicating an unmet demand for access to fexofenadine from grocery outlets.

- Noted that the October 2009 meeting acknowledged that fexofenadine was safe when used as directed.
- Asserted that the application demonstrated that the benefits of broadening availability of fexofenadine outweighed the potential risks.

Evaluation Report

The evaluation report noted that this matter had been previously evaluated and considered by the NDPSC in October 2009. The evaluator noted that much of the current application drew on references that had been submitted previously. The present (2011) evaluator generally supported the conclusions of the previous evaluation and agreed that the submitted information was not sufficient to support an exemption from scheduling for small preparations of fexofenadine (i.e. recommended no change to the current scheduling). The 2011 evaluator also made the following points:

- Noted that there was little information about the ability of sufferers to accurately diagnose that they have SAR. Noted that the application claimed not that misdiagnosis was unlikely, but that it was unlikely to have an impact on the progression of more serious diseases. Asserted that in spite of a lack of symptom relief, the individual may continue to take the antihistamine.
- Noted information from a large US epidemiological study where the authors stated that results were consistent with no large increased risk for birth defects associated with antihistamine use during early pregnancy. The results were generally reassuring about first trimester exposure to antihistamines, and especially second generation antihistamines.
- Asserted that spontaneous reporting, as summarised in recent Periodic Safety Update Reports, did not add any concern about an association between first trimester use and birth defects.
- Noted that results of a survey have been submitted to support that consumers, especially pregnant women, always read label warnings the first time they purchase a medicine. The evaluator had concerns about the lack of methodological detail and that the results were not accurately reported in the submission. A reference submitted in the application about the transfer of orally ingested terfenadine to breast milk supported that the extent was very low and unlikely to be associated with adverse symptoms in the infant.
- Asserted that there was no additional information, beyond the expressions of opinions in the Supporting Statements, to show that there was a need for greater access and that such access would lead to greater benefits among patients with SAR (or the community in general).

The evaluator also reiterated many points from the previous evaluation report and provided a number of additional comments, summarised below:

Toxicity and Safety

- The applicant noted that as the NDPSC in its previous consideration regarded fexofenadine as generally a safe drug, only a brief summary of data was provided in the present application.
- The applicant cited the revised product information in support of a claim that "Clinical studies for up to 12 months showed no significant change in safety or tolerability when compared to placebo." In fact, the product information statement related only to significant changes in the QTc interval.
- Overall the evaluator accepted that the safety profile of fexofenadine was well established and that no new safety signals had emerged.

Risks and Benefits

- The submission included two new reviews not previously available to the NDPSC which concluded that symptoms of allergic rhinitis were likely to be much more intense nocturnally, during intended sleep, and/or in the early morning on awakening. The results of the reviews were reasonable. They were presumably submitted to support the proposition that there is a need for twenty-four hour access to supplies of fexofenadine.

Potential Hazards

- The submission referred to the results of an online survey completed by 150 pharmacists which reported that "37 per cent of consumers presenting to the pharmacist seeking SAR medication do so as a result of self-diagnosis. Of these consumers, 67 per cent successfully self-diagnosed and only 33 per cent needed further assistance. It should be noted that the 33 per cent of consumers needing further assistance were not necessarily considered to have misdiagnosed their condition." The evaluator could not find any description of the criteria by which the pharmacist was to judge correct self diagnosis.
- New references were submitted with descriptions of the symptoms of the common cold, infectious rhinitis, chronic sinusitis (said to have a prevalence in Australia of about 10.5 per cent), and nasal tumours. These descriptions were provided in support of the application's claim that if misdiagnosis occurred, it would be unlikely to impact the progression of more serious diseases and a 5 day delay in consulting a healthcare professional would not result in clinically significant events. These disease descriptions did not provide robust information about how frequently other conditions were diagnosed as SAR, and the clinical consequences of such misdiagnosis.
- Regarding effects in pregnancy, the submission referred to the results of epidemiological data of US birth defects published in 2009. The detail of this study indicated that it was <u>not</u> correct to state, as in the submission, that no association was identified. Twenty three weak to moderate magnitude associations and one strong but

imprecise association with antihistamine exposure were identified (eight involving diphenhydramine). The results were generally reassuring about first trimester exposure to antihistamines, and especially second generation antihistamines. There were, however, relatively few exposures to fexofenadine in the case and control subjects. The authors stated that the results were consistent with no large increased risk for birth defects associated with antihistamine use during early pregnancy.

- The applicant stated that from March 2005 to March 2009 a total of 127 drug exposures were reported in pregnant/breastfeeding women. Of these, 74 were medically confirmed cases; and 6 exposures were classified as serious adverse events. The evaluator was not able to verify these findings, as the bridging report covering much of the period did not include such information. The evaluator could identify records of 24 medically confirmed "drug exposures via the parent". It was noted that a September 2008 to March 2009 report associated the birth of an infant with syndactyly of the feet with daily ingestion of fexofenadine for allergy during the first six weeks of pregnancy. The evaluator regarded that report as having little significance as there was a high possibility of a chance association.
- The application referenced a study of terfenadine in breast milk. The evaluator accepted that the newborn exposure should be low, and not result in plasma concentrations producing untoward effects in the baby.
- The application contained statements from general practitioners and pharmacists concurring that broader access to fexofenadine would not pose any higher risk to pregnant or breastfeeding women than a number of existing medicines available through grocery channels. These letters did not include information as to how the authors came to provide the independent supporting statements to the applicant nor cited references in support of their views.
- A similar view about the acceptability of wider access was expressed by a Clinical Pharmacologist XXXXX who disclosed that he has been reimbursed by the applicant to provide a supporting statement. Concerning safety in pregnancy, this support rested on the current B2 categorisation and that there were clear warnings on the packaging and in the CMI. Members noted that XXXXX also provided a pre-meeting submission which was summarised in the relevant section below.
- A supporting statement provided by XXXXX stated that about one third of XXXXX suffer from hayfever. It was submitted that urgent access to treatments in the evenings or early mornings when pharmacies were closed was needed to allow hayfever sufferers to keep on top of their symptoms and to function as effectively as possible on a day-to-day level. Members noted that XXXXX also provided a pre-meeting submission summarised in the relevant section below.

Labelling and presentation

- The applicant proposed additional / clearer warning statements to those already included in the Schedule 2 presentations:

- *This product should not be used when pregnant or when breastfeeding except when advised by your Doctor or Pharmacist*
- *Do not use in children under 12 years.*
- *Do not take more than the recommended dose.*
- *Do not use with other antihistamines.*
- *If symptoms persist after 5 days, consult your Doctor or Pharmacist.*
- *Keep out of reach of children*

· A pictorial representation of a pregnant woman was included to further highlight this warning and to facilitate comprehension by patients with lower literacy skills. Additionally, the statement '*Read the enclosed leaflet for additional information*' and the 'freecall' telephone number listed on the labelling gave two additional sources of information on the product.

· The applicant referred to the results of a survey to support the claim that at least 93 per cent of consumers read label warnings the first time they purchased a medicine, with an even greater proportion of pregnant women agreeing they always read warning labels and are careful to do so. The evaluator asserted that the methodology of the research was poorly described and that some of the interpretations by the applicant were overstatements.

Need for access

· The 2009 evaluator noted that the evidence provided was reasonable to support a safety/tolerability advantage of fexofenadine over three other second-generation antihistamines (loratadine, desloratadine and cetirizine - none of which are currently unscheduled).

· The 2009 evaluator also stated that while a greater safety/tolerability profile of fexofenadine over available alternatives mounted a case for first-in-class exemption from scheduling, the application did not provide evidence that there was a need for greater access.

· The 2011 evaluator noted that no new information had been presented in relation to need for access.

Purpose of use

· Noted the 2009 evaluator's comment that of all patients presenting to pharmacists seeking medications for SAR, at least two-thirds did not self-diagnose SAR. The applicant argued that because these patients received advice from a healthcare professional, they would be unlikely to use SAR medications inappropriately. The evaluator asserted that this only highlighted the need for input from a healthcare professional, without which up to two-thirds of SAR medication users would be at risk of inappropriate use.

- The 2011 evaluator noted that no new information had been presented in relation to purpose of use.

Applicant's Response to the Evaluation Report

XXXXX provided a response to the evaluation report, summarised below. Part of this response relied on data not contained in the original application.

Misdiagnosis

- Acknowledged the concerns raised by the evaluator that in spite of a lack of symptom relief, an individual may continue to take fexofenadine. Argued that in assessing the risks in practice it was not considered that there was any greater risk to consumers based on the availability of a small pack size of fexofenadine compared to risks posed by other medicines that were widely available through grocery channels, including those commonly used for pain relief e.g. paracetamol, aspirin and ibuprofen. Contended that there was a greater potential for harm from these agents, however these risks have been effectively mitigated by controls on pack size and appropriate labelling. Asserted that the same approach would be equally valid to address any potential concerns relating to fexofenadine.
- Asserted that as SAR is a chronic condition for many patients there is a high level of awareness and knowledge relating to symptoms and treatment. Stated that it would be these patients who were most likely to seek access to therapy 'out of hours' to assist with quick symptom relief. A pharmacist would continue to remain the primary point of call for SAR patients newly experiencing symptoms of SAR who were unfamiliar with available treatment options or who were actively seeking advice from a Health Care Professional (HCP).
- Stated that in SAR a definitive diagnosis is derived through allergen testing, however patients can and do recognise the symptoms of the condition. Asserted that the long-term availability of SAR treatments in NZ and in the UK outside of pharmacies reflects the ability of SAR patients to self-diagnose and choose appropriate treatment options. Stated that the desired outcome of a 5 day/low dose fexofenadine course was for short term symptomatic control and not allergy therapy. Asserted that the signs and symptoms of SAR which impair quality of life necessitate the need for immediate access of fexofenadine.

Pregnancy and Breastfeeding

- Mentioned that the revised warning statements on the package and the existing availability of products in grocery that have higher pregnancy categories also support the lack of risk from fexofenadine. Claimed that this matter was adequately addressed.

Access

- Acknowledged the evaluator's feedback in relation to the survey data included in the application. Highlighted that the medical justification robustly supported the rationale for broader community access to fexofenadine, to allow patients to rapidly manage otherwise debilitating symptoms. Stated that this view was reflected in supporting statements from experienced practitioners in the field.
- Considered that the evidence for the need for broader access to fexofenadine met the required criteria for exemption from scheduling. Stated that the acute onset of SAR symptoms and need for rapid access to effective treatments could be compared to the need for rapid access to medications to treat acute pain, available through grocery channels.

Package leaflet

In response to the evaluator's comment on the inadequacy of the proposed patient leaflet for an unscheduled drug due to the 'constant reference to consulting a pharmacist' in any instance of potential unsuitability (eg pregnancy) or problem encountered with use of fexofenadine, the applicant contended:

- Although the majority of products such as pain relief medications available through grocery channels were not supplied with a leaflet, providing consumers with more detailed readily accessible information would support quality use of medicines. The CMI format was chosen as it was familiar to consumers and was the accepted format for providing consumer friendly information.
- That the statements in the CMI were not focused on consultations with a pharmacist, rather recommendations to seek medical advice in specific instances. For example 'If symptoms persist after 5 days consult your doctor or pharmacist'. These statements were no different in nature to statements included on pain relief medications such as paracetamol, aspirin or ibuprofen in a shortened version also relating to seeking medical advice under various relevant circumstances e.g. if asthmatic. Argued that since there was more space on the CMI, a conservative approach was taken with the level of communication and reference to HCPs, however did not imply the need for a HCP to be involved to ensure appropriate selection of medication.

Based on the above, the applicant stated that it will consider any recommendations from the ACMS to revise the CMI text accordingly.

NEW DATA / INFORMATION

Members noted that the applicant included new data in its response to the evaluation report which had not been assessed by the evaluator. However, Members also noted that many of the arguments referencing this new data were raised previously in the application.

The applicant stated that in considering the suitability of fexofenadine for broader access through grocery channels, comparison of its usage profile to that of other widely available medicines was of relevance:

- Ranitidine, available for relief of heartburn and indigestion could potentially mask gastric carcinoma symptoms, however it was generally accepted as safe for use in short term relief of symptoms.
- Medicines used for pain relief such as aspirin, ibuprofen and paracetamol were commonly purchased in grocery channels. In this category there were many potential risks that self-medication will mask a more serious condition e.g. minor fracture, muscle tears and joint damage where the clinical consequences were that more damage could result due to failure to take the appropriate measures at the time of the initial injury.
- In contrast, patients exposed to fexofenadine were at minimal risk that more serious underlying causes such as polyps, chronic sinusitis or nasal tumours would be masked or the natural course of disease progression would be altered in any substantive way. Moreover, the safety profile of fexofenadine presented negligible risk to consumers who may inadvertently misdiagnose SAR and consequently gain no benefit from a 5 day treatment course.

Further 'additional' data referred to reviews of non-prescription analgesics conducted by the TGA. The applicant's response stated that the reviews had highlighted a number of safety concerns for analgesics such as accidental poisoning or self-poisoning, potential toxicity in alcoholics with paracetamol, use in the last three months of pregnancy for aspirin and paracetamol and risk of gastric bleeding with aspirin. Stated that management of any risk through the introduction of appropriately sized and labelled packs including advice on when to seek medical advice had been acceptable for products in the grocery channel. Asserted that this same approach had been used in many other countries which have rescheduled OTC medications and have mitigated risk from chronic use or misdiagnosis by limiting the pack size and the dosage. Concluded that the proposed labelling for fexofenadine advising consumers to consult their doctor or pharmacist if symptoms persist after 5 days was a suitable risk mitigation approach for fexofenadine to address any potential for misdiagnosis.

October 2009 NDPSC Discussion

The NDPSC reiterated the 2009 evaluator's concerns over the potential use of fexofenadine by pregnant or breastfeeding women, noting that fexofenadine was in Pregnancy Category B2 and there were uncertainties as to the amount of fexofenadine that entered the breast milk. It was asserted that to exempt fexofenadine from scheduling would not be appropriate until these uncertainties had been resolved.

A Member noted that other antihistamines, such as loratadine, were currently listed in Schedule 2 yet had lower pregnancy risk classifications. It was noted that labelling

would not appropriately address these concerns as such warning would not be noticed by some people on the assumption that any medication on unrestricted sale must be safe.

A Member also suggested, in terms of the argued need for out-of-hours access, that hay fever was seasonal and that it was reasonable to assume suffers would anticipate SAR onset and have antihistamines on hand. Other Members disagreed, noting that SAR could have rapid and unexpected onset.

The NDPSC noted the evaluator's concerns over the potential for misdiagnosis of SAR versus conditions such as infectious rhinitis, chronic sinusitis, nasal polyps and nasal tumours. Members noted that the findings from the application stated only 'two out of three' people could correctly self-diagnose SAR. A Member asserted that a Schedule 2 listing would help to ensure that appropriate counselling would be available to assist with diagnosis.

The NDPSC asserted that the application did not provide sufficient data to establish a significant benefit in exempting fexofenadine from scheduling and that the benefit from access out-of-hours did not outweigh the central safety concerns relating to pregnancy

February 2010 NDPSC Discussion

The NDPSC 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.

In relation to out-of-hours access, Members asserted that access was already adequate noting extensive pharmacy opening hours and existing jurisdictional arrangements to allow access to Schedule 2 medicines in 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. A 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, given the current lack of knowledge about possible adverse effects from fexofenadine use in these cases. Other Members contended that this issue should not be of major concern, given the much greater risk posed by other medicines which women could routinely be using in early pregnancy when they were not aware they were pregnant.

February 2011 Pre-meeting Submissions

Pre-meeting submissions supporting the applicant's proposal were received from XXXXX.

Pre-meeting submissions from XXXXX did not support the applicant's proposal and recommended that the current scheduling remain unchanged.

The main points from these submissions are summarised below:

XXXXX

- Asserted that there was demonstrated benefit for extended access to treatments for other ailments (cold and flu, nicotine replacement, heartburn relief and pain relief) where availability through grocery channels led to faster initiation of treatment.
- Increasing access to small, low dose packs of fexofenadine would allow consumers to better manage their SAR.
- Were confident in the ability of the grocery sector to manage the distribution of these products appropriately.

XXXXX

- The resulting fatigue associated with hayfever could severely affect a sufferer's ability to function (i.e. productivity, safe driving, child care).
- Extended access to treatments through supermarket channels for when symptoms arise was an important step in helping sufferers maintain control of the condition.
- Similar to allergy sufferers, people with hayfever were familiar with their symptoms, had a good understanding of their condition, were capable of self-treatment and would treat themselves during the hayfever season with minimal interaction with a pharmacist.
- Fexofenadine products have been available for a very long time and were a well-known and effective treatment for hayfever.
- Fexofenadine had a safer use pattern than other medications available in grocery outlets.
- An exemption from scheduling would allow for sufferers to more effectively manage their condition during the hayfever season.

XXXXX

- Noted that fexofenadine was well tolerated in recommended doses and had a long history of safe and effective use as a Schedule 2 drug.
- Stated that nuisance side effects in small numbers of patients were noted in the PI and these have not been distinguishable in number from placebo treatment in controlled trials.
- Asserted that information on the medicine, the proposed directions for use and warnings against using the drug in pregnancy and during breastfeeding have been highlighted clearly and more explicitly on the packaging and in the CMI. Noted that the proposed packaging also communicated advice on consultation with a pharmacist in cases where resolution of symptoms was unsatisfactory or untoward effects were suspected.
- Reiterated that medicines with more concerning pregnancy warnings were available through grocery channels e.g. aspirin and ibuprofen.
- Asserted that no new data had emerged regarding potential hazards of fexofenadine in pregnancy and to the foetus. Stated that studies in animals show no evidence of an increased occurrence of foetal damage.
- Asserted that there were no new data in relation to fexofenadine use during breastfeeding in addition to that found in the PI. Noted the results of a study which examined the pharmacokinetics of the drug in lactation. Quoted the study's conclusion that:

  > *"Newborn dosage estimates based on the highest measured concentration of terfenadine metabolite in milk suggests the maximum level of newborn exposure would not exceed 0.45 per cent of the recommended maternal weight-corrected dose. Estimated amounts consumed by the neonate after the mother is given the recommended dose of the drug are not likely to result in plasma levels producing untoward effects."*

- Asserted that the argument for access through grocery channels for limited supply of fexofenadine rested on the significant and distressing symptoms associated with SAR, the associated decrement in quality of life of sufferers and the benefits associated with timely antihistamine use.

XXXXX

- Reiterated earlier points on the demonstrated safety of fexofenadine in toxicological studies and clinical trials and the history of safe and effective use.
- Noting the exception for pregnant and breastfeeding women, asserted that fexofenadine was generally well tolerated among the majority of hay fever sufferers.
- Noted that the acute onset of SAR symptoms often occurred outside normal business hours, where access through grocery stores would be necessary.

- Reiterated previously made comments on improved clarity of the information included in the proposed packaging and the role of labelling in the referral for pharmacist advice.
- Stated that both pharmacy and grocery sectors share the responsibility for patient management, where the grocery sector has played an important role in assisting Australian consumers to manage a variety of conditions such as headaches, general pain, coughs and colds, heartburn and smoking cessation.
- Reiterated the previously made point that products with higher pregnancy classifications were currently available in supermarkets.
- Noted that small preparations of fexofenadine were currently available in supermarkets in NZ and the UK.

XXXXX

- Noted the lack of opportunity for pharmacist advice for unscheduled versus Schedule 2 products. Stated that new users could be attracted to the smaller packs in grocery to "try" the medicine if they have symptoms suggestive of SAR and would not have access to appropriate advice. Stated that repeat purchasers may be more likely to buy the larger pharmacy-only packs.
- Asserted that the symptoms of SAR could be confused with other conditions, such as common cold and chronic rhinitis or non-allergic rhinitis. In these situations, a pharmacist's advice was necessary to aid correct diagnosis. Stated that other situations such as pregnancy, breastfeeding, and use with antacids may also require a pharmacist's advice.
- Asserted that an exemption for fexofenadine would instigate sponsors of other second generation antihistamine products to apply to also exempt their product. Stated that the presence of fexofenadine in grocery stores could lead to consumers assuming that this product was "safer" than its pharmacy-only competitors. Asserted that in making a recommendation, the ACMS should consider the "landscape" of the different products within the same class, not only the individual medicine, so that consumers would not have a misleading impression of the safety of one product over the others.
- Noted that fexofenadine was not associated with a sedation warning and stated that in NZ all second generation antihistamines are required to be labelled with *"Although the medicine is unlikely to affect your ability to drive or operate machinery, a few people may be impaired and care should be taken."*
- Stated that a class-wide approach to label warnings would advise consumers of the risks associated with a given product. Members noted that as the delegate's proposal did not mention an Appendix K entry, consultation had not occurred for such a proposal.

XXXXX

- Noted that SAR was a common presentation in pharmacies and there were numerous products available to effectively manage symptoms. Noted that the condition could usually be recognised by consumers and was suitable for short-term, self-treatment.
- Asserted that there were circumstances which necessitated professional intervention, including the provision of information and counselling at the time of supply of a product when other causes may be suspected, when original symptoms had not resolved after a few days, in cases of reported reliance (more than intermittent use) on a medication intended for short-term treatment, and/or when referral to a medical practitioner was warranted.
- Stated that the current scheduling allowed fexofenadine in preparations for oral use to be made available to consumers from an environment where advice and intervention could be provided at the time of purchase of the product or during a period of follow-up and monitoring. Asserted that this was vital from a patient safety perspective and to ensure optimal use of medicines and that these safeguards would not be available to consumers if the substance was exempted (regardless of any warning statements included through product packaging and labelling).

XXXXX

- Noted claims on consumers' ability for self-diagnosis of SAR provided as part of the NZ MCC consideration of the scheduling of fexofenadine. Stated that SAR treatments were available through pharmacies where patients have been supported by professional pharmacist advice when needed, hence assisting self-diagnosis.
- Stated that SAR was not a benign condition that should be left to patient self-diagnosis or self-management and there were potentially serious consequences that could result from incorrect diagnosis or improper management.
- Noted data from the National Asthma Council Guidelines stating that 20-30 per cent of patients with known allergic rhinitis also have asthma and that patients can mistake symptoms of allergic rhinitis for asthma.
- Noted data from a 2006 European report stating that 40-50 per cent of patients with allergic rhinitis suffered from asthma and more than 90 per cent of asthmatics also had rhinitis. Noted that chronic nasal congestion may result in rhinosinusitis and the obstruction of sinus ostia due to infections predisposed by negative pressure and mucous stagnation and that nasal polypsis may result from the chronic inflammation of nasal mucosa.
- Stated that severe SAR episodes warranted HCP intervention as patients may experience sleep disturbance, impairment of daily activities or participation in leisure or sporting activities as well as impairment of school or work activities.

- Asserted that pharmacists and pharmacy assistants undertake training on how to triage patients and when to refer to the pharmacist, to recommend a more appropriate course of action, or to refer to a general practitioner.
- Stated that should fexofenadine be exempted from scheduling, there would be no support available to assist the patient or to intervene should the patient be selecting multiple packs of fexofenadine or purchasing it in combination with other products which, in a pharmacy, would likely prompt referral to the pharmacist (e.g. decongestant nasal spray, decongestant tablets, lozenges).
- Stated that intranasal corticosteroids were more effective than antihistamines in controlling symptoms of allergic rhinitis as well as non-allergic rhinitis and treatment of allergic rhinitis with intranasal corticosteroids reduced the risk of asthma-related emergency department visits and hospitalisation in patients with asthma and coexisting allergic rhinitis and may improve lung function. Asserted the importance of access to HCP advice for people with SAR who may have undiagnosed or uncontrolled asthma to assess symptoms and recommend the most appropriate course of action.
- In relation to a claim regarding the economic burden of the prevalence of SAR, stated that pharmacist intervention was a safety check mechanism that could alleviate this economic burden. Stated that there could be an even greater adverse impact on the economy if patients with more severe forms of SAR or with other co-morbidities were to self-diagnose and self-treat their condition without access to appropriate intervention.
- Asserted that anecdotal reports from the 2010 hay fever season indicated that many patients reported that usual second-generation antihistamine treatment was not as effective, and that alternative or additional therapies were required or patients have increased the dosage of their own accord in response to the lack of perceived efficacy.
- Asserted that it was more cost-effective to have free and easily accessible professional advice from a community pharmacist based on the symptoms presented and medicine history, than to select products off a supermarket shelf for trial and error.
- Stated that the primary concerns related to the safety of fexofenadine use in at-risk groups (i.e. pregnant women). Asserted that it was not appropriate to rely solely on label warnings to caution against the use of fexofenadine in pregnancy due to the public's levels of health literacy. Noted data which indicated that from a range of 5 levels for health literacy, when examined by age, only 48 per cent of females aged 15-44 years achieved health literacy of Level 3 or above.
- Noted extended opening hours of pharmacies in Canberra and asserted that urgent treatment from a pharmacy could be accessed within a nine to fourteen hour period if needed. Asserted that other metropolitan areas would have similar arrangements and noted that states and territories have special licensing arrangements in place for Schedule 2 medicines to be available in areas without access to a pharmacy.

- Noted the availability of many products containing fexofenadine and other second-generation antihistamines for the treatment of SAR and stated that with such competition there was not a strong argument that increasing access from other sectors would significantly reduce the retail price of these products.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members noted that the application under consideration was similar to the previous submission considered by the NDPSC at its October 2009 meeting. Members noted new content regarding effects in pregnancy and proposed label warnings.

A Member noted the high concurrence of SAR with asthma. Members discussed claims of a link between the treatment of allergic rhinitis with inhaled corticosteroids and a reduction in hospitalisation from asthma. However, other Members noted that the studies reported may have contained confounded data and a closer examination of the research was warranted. A Member asserted that retaining SAR treatments in the pharmacy situation where appropriate questioning could occur would help in eliciting whether concurrent asthma was present and allow the consumer access to the full range of SAR treatments (including inhaled corticosteroids).

A Member reasserted the NDPSC's concerns regarding consumers' limited ability to accurately diagnose SAR, and the risks of fexofenadine masking more serious conditions. Other Members noted, however that there were medicines currently available as unscheduled in small packs which also carried this risk (i.e. paracetamol). The Member asserted that the submission assumed consumers would only buy 5 days' supply. Another Member noted that this risk was present with other unscheduled medicines and consumers would seek professional advice if their condition was not resolved within an appropriate timeframe.

A Member reiterated a submission's comment that pharmacy assistants were trained to triage patients and provide advice on the range of available treatments and that this safety measure would not be available in grocery channels. The Member raised concerns over the risk-benefit balance in these situations where consumers would not have access to the whole spectrum of treatments available and would have to rely solely on information from advertising and labelling. It was stated that the availability of only one form of treatment may result in inappropriate treatment of SAR. However, another Member asserted that chronic sufferers would already be informed of the appropriate treatments for their symptoms and the availability of small packs of fexofenadine in grocery channels would provide additional benefit by allowing greater access in urgent cases. Another Member further stated that patients with no history of SAR who experience a first attack would present to a pharmacy for appropriate advice where there would be access to the full range of available treatments.

Members noted a pre-meeting submission's comments on the opening hours of pharmacies in metropolitan areas. A Member asserted that 24 hour access to fexofenadine was not required and existing pharmacy opening hours were sufficient for

urgent access to fexofenadine if needed. The Member further asserted that although pharmacies in rural areas did not have extensive opening hours, the opening hours of grocery outlets were also not extensive. The Member stated that even if small packets of fexofenadine were exempt from scheduling, there was no guarantee that these products would be stocked in small rural community outlets. However another Member stated that any increase in the opening hour availability of a "rescue medicine" like fexofenadine would provide benefit to the public.

Members noted that fexofenadine was available in grocery outlets in a majority of comparable countries worldwide with no evidence of an increase in harm. The majority of Members agreed that, on balance, increasing access in Australia to fexofenadine for the treatment of SAR in small packs could provide benefit to the public and was not likely to result in an increase in harm.

Labelling

Members discussed the risks associated with the use of fexofenadine in pregnancy and breastfeeding. A Member noted recent data indicating that the risks of fexofenadine use in pregnancy was lower than previously expected, however asserted that this was still an issue which needed to be addressed. Members noted that there was no requirement for unscheduled products to contain a CMI.

A Member noted that currently the Schedule 2 presentation of fexofenadine contained warnings on the use of the medicine in pregnancy, however did not mention use in lactation. The Member asserted that lactation was also a concern and consistency with regard to labelling should be maintained between Schedule 2 and any unscheduled fexofenadine products.

Members noted that with the implementation of revised scheduling arrangements, the delegate may refer a recommendation from the ACMS for appropriate label warnings for over-the-counter medicines to appropriate areas within the TGA. Members generally agreed that a recommendation for appropriate labelling through the *Required Advisory Statements for Medicine Labels* should be considered and that these labels should be consistent between Schedule 2 and unscheduled presentations of fexofenadine.

Implementation date

Members noted that the delegate's final decision associated with this matter was expected to be published in June 2011. Members generally agreed that there was no need for a delayed implementation date and recommended an implementation date of 1 September 2011 (three months following publication of the delegate's final decision).

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate specifically noted the efficacy of fexofenadine

preparations in the treatment of SAR. The delegate agreed with the Committee's recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (d) labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to exempt fexofenadine from scheduling when for the short-term symptomatic relief of seasonal allergic rhinitis in adults and children 12 years of age and over when sold in small packs of 10 dosage units or less (i.e. not more than 5 days supply at the current maximum recommended dose) with a maximum daily dose of 120 mg. The delegate decided on an implementation date of 1 September 2011.

The delegate also decided to recommend to the appropriate areas of the TGA consideration of a requirement for a labelling warning statement in the *Required Advisory Statements for Medicine Labels* for exempt preparations of fexofenadine to the following effect:
"This product should not be used when pregnant or when breastfeeding except when advised by your Doctor or Pharmacist. Do not use with other antihistamines."

SUBMISSIONS ON INTERIM DECISION

Two further submissions were received from XXXXX opposing the interim decision and stating that the current scheduling of fexofenadine should remain unchanged. The submissions also made several points, summarised below:

XXXXX

- Noted that Quality Use of Medicines (QUM) was one of the central objectives of Australia's National Medicines Policy and asserted that QUM was best supported by the supply of medicines through a pharmacy with access to specialised professional support and advice from a pharmacist. Hence have traditionally opposed exempting medicines from scheduling stating concerns that the proposed arrangements may facilitate use of medicines in a manner that does not align with QUM principles.
- Reiterated that there were no controls or quality assurance processes in place for supply of medicines through the grocery channel and customers with chronic conditions could purchase multiple small packs without any questions asked about the condition, patient history or medicine use. Reasserted that access through the pharmacy sector was more than adequate and provides access to health professional advice to support QUM objectives.
- Reasserted that triaging for HCP intervention was essential as chronic SAR or SAR with complications warranted investigation. Stated that risk factors associated with fexofenadine use warranted pharmacy sector management.

- Reiterated that it was important to protect vulnerable patient groups such as the young, elderly and people whose first language was not English. Asserted that the inclusion of warnings and directions on packs did not surmount the issues associated with poor consumer health literacy without the opportunity for counseling.
- Noted the ACMS' comments regarding links between SAR and asthma and reiterated concerns that it was essential that people suffering SAR symptoms were exposed as much as possible to HCP intervention. Stated that internationally, Australia has the second highest incidence of asthma and 40 per cent of Australians have an allergic disease. Supported further investigation of relevant research however asserted that the current evidence should not be dismissed due to significant potential consequences.
- Noted the applicant's examples of other substances currently unscheduled and stated that it was dangerous practice to introduce the idea of 'precedents' in the review of substances requesting exemption. Asserted that each application must be considered on its own merits regarding the substance's use and safety profile. Stated there was no information on whether there were potential problems in pregnancy and breastfeeding associated with the other substances currently available as unscheduled.
- Raised concerns regarding the quantities available in the proposed unscheduled 'rescue pack'. Stated that 'rescue packs' should be solely to provide short-term relief without delaying access to professional advice and asserted that a pack containing more than 24 hours therapy was not a 'rescue pack' with unrestricted access discouraged. Suggested that exempt fexofenadine should be restricted to 24 hours therapy.
- Disagreed with a Member's comment that chronic SAR sufferers would consult a HCP for larger pack sizes and argued that sufferers could instead buy multiple packs from a grocery outlet. Noted progress on systems used to record non-prescription medicine use and stated support for the recording of treatments against a patient's profile for chronic conditions such as SAR.
- Raised concerns regarding the small sample size of consumers presenting to the pharmacist as a result of self-diagnosis reported in the survey included in the application.
- Asserted that while chronic SAR sufferers may be considerably aware of their condition, in line with QUM principles, they would still benefit by having access to balanced, accurate, evidence-based, current advice about the most appropriate manner to manage their condition. Reiterated that pharmacist would be able to triage patients with other co-morbidities and refer or provide medical certificates if required.
- Noted data from a US survey on the treatment and prevention of allergy-related symptoms, where adult antihistamines accounted for 32 per cent of pharmacists recommendations. Other recommendations included decongestants, ophthalmic drops, multi-symptom products, expectorants and breathe-right strips.

- Reiterated points from the pre-meeting submission regarding need for HCP intervention; severity of the 2010/2011 SAR season; and treatment of people unfamiliar with SAR. Disagreed with a Member's comment regarding new SAR sufferers presenting to a pharmacy in the first instance.
- Asserted that through the use of promotional displays the grocery channel may target people unfamiliar with SAR and/or the availability of alternative treatments. Stated that it was likely that in the grocery setting fexofenadine products would be grouped with oral and topical nasal decongestants as well as decongestant eye drops. Asserted that patients familiar and unfamiliar with SAR suffering from nasal and ophthalmic symptoms could select these additional products inappropriately due to a lack of advice.
- Stated that self-selection of medicines for initial trail would not be cost-effective for consumers if the product did not work.
- Noted an Irish study investigating the purchase of paracetamol in non-pharmacy outlets in quantities of either 2 x 24 packs or 4 x 12 packs. Stated that this demonstrated that purchases were made in each outlet without difficulty or questions from sales assistants, even though there was commentary on the researcher's presumed poor health.
- Noted a pre-meeting submission asserting the role played by the grocery sector in management of various health conditions and asserted that the grocery sector also supplies products which cause or aggravate these conditions.
- Noted the application's assertion that exempt fexofenadine would be for short term symptomatic control and not allergy therapy. Stated that there was no way to control the condition that the product was used for. Reiterated concerns regarding the use of fexofenadine for severe allergic reactions appropriate risk mitigation.
- Reiterated comments regarding the extensive opening hours of pharmacies and asserted that in some jurisdictions, regulations for store trading hours mean that after-hours pharmacy access is as good as or better than that through the grocery sector. Provided details of opening hours in certain metropolitan areas. Noted pharmacy after-hours access allowances for regional areas.
- Reiterated concerns about use of labeling to address risks and levels of health literacy. Noted Australian Bureau of Statistics survey results indicating that a number of Australians (including people whose language was not English) did not have sufficient literacy skills to meet the complex demands of everyday work and life, and that on the health scale, 60 per cent attained scores below the minimum requirement to meet everyday needs. Raised specific concerns in relation to pregnant or breastfeeding young women from lower socio-economic areas.
- Reiterated concerns regarding misdiagnosis and consequences of delays in seeking appropriate advice.

- Queried the use of a revised CMI and how this will be available in the grocery setting. Specifically queried whether it will be included in the pack and whether it will be a requirement for all sponsors.

XXXXX

- Noted that this was the third consideration of a proposal to exempt fexofenadine within two years. Stated that apart from the recommended requirement for pregnancy labelling there was no new evidence to support an exemption.
- Reiterated points from the pre-meeting submission regarding appropriate professional intervention at the time of supply and on follow-up when original symptoms have not resolved after a few days. Asserted that supply of fexofenadine from an environment that does not afford this opportunity was not consistent with promoting quality use of medicines and therefore, not in the best public interest.
- Asserted that access to non-prescription medicines from community pharmacies where professional intervention was available has been shown to help avoid adverse events and further costs to the health care system.

DELEGATE'S FINAL DISCUSSION

The delegate considered the two submissions received in response to the interim decision and noted that it reiterated many points which were previously raised in pre-meeting submissions which were considered as part of the ACMS's and delegate's interim discussions.

The delegate again noted ACMS Members' discussion of the risks and benefits of fexofenadine when exempt from scheduling, specifically the preparation's efficacy in the treatment of SAR.

The delegate agreed that the interim decision was appropriate and that small preparations of fexofenadine (up to 5 days supply) for the short-term symptomatic relief of seasonal allergic rhinitis in adults and children 12 years of age and over should be exempt from scheduling.

DELEGATE'S FINAL DECISION

The delegate confirmed that fexofenadine when for the short-term symptomatic relief of seasonal allergic rhinitis in adults and children 12 years of age and over when sold in small packs of 10 dosage units or less (i.e. not more than 5 days supply at the current maximum recommended dose) with a maximum daily dose of 120 mg should be exempt from scheduling. The delegate also confirmed an implementation date of 1 September 2011.

The delegate also decided to recommend to the appropriate areas of the TGA consideration of a requirement for a labelling warning statement in the *Required Advisory Statements for Medicine Labels* for exempt preparations of fexofenadine to the following effect:
"This product should not be used when pregnant or when breastfeeding except when advised by your Doctor or Pharmacist. Do not use with other antihistamines."

Schedule 2 – Amendment

FEXOFENADINE – Amend entry to read:

FEXOFENADINE in preparations for oral use **except** in preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

(a) in a primary pack containing 10 dosage units or less; and

(b) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

Schedule 4 – Amendment

FEXOFENADINE – Amend entry to read:

FEXOFENADINE **except**:

(a) when included in Schedule 2; or

(b) in preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

(i) in a primary pack containing 10 dosage units or less; and

(ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

2.1.3 IBUPROFEN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of ibuprofen and decided to seek advice from the ACMS on the following:

Ibuprofen - to increase the maximum allowable pack size of ibuprofen in liquid preparations in Schedule 2 from 4 g to at least 8 g.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended increasing the maximum allowable amount of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8 g. The Committee also recommended an implementation date of no more than 6 months following the delegate's final decision (earliest 1 September 2011).

BACKGROUND

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used as an over-the-counter (OTC) analgesic and anti-inflammatory agent for minor self-limiting conditions, including inflammation, pain or fever. Historically, liquid formulations of ibuprofen have also been used for the treatment of children with acute, self-limited conditions such as toothache, colds and flu, headache and minor sprains and strains.

Ibuprofen was first included in Schedule 4 in February 1973.

In November 1998, the NDPSC considered an application to down-schedule liquid ibuprofen to Schedule 2. The NDPSC agreed that Schedule 3 would be more appropriate at that time, to ensure that pharmacist advice would be available. Ibuprofen liquid preparations were included in Schedule 3 with a maximum recommended daily dose of 1200 mg, but no specific maximum total content. At that time products available on the market included suspensions in a total pack volume of 200 mL containing a total of 4 g ibuprofen.

In February 1999, the NDPSC considered a recommendation from the Trans-Tasman Harmonization Working Party that ibuprofen suspension should be included in Schedule 2 to harmonise with New Zealand scheduling. This was supported, and the resulting Schedule 2 entry, with regard to liquid preparations, included a maximum volume (200 mL) and a maximum strength of 100 mg/5 mL (20 mg/mL, or 2 per cent). Although a maximum total quantity for liquid preparations was not specified, this combination of maximum volume and strength in effect provided for a maximum total quantity of 4 g.

In May 2000, the NDPSC considered an application requesting alteration of the Schedule 2 ibuprofen entry to include oral liquid preparations containing more than 20 mg/mL of ibuprofen. The application argued that such preparations would have qualified as Schedule 3 products prior to the Trans-Tasman harmonisation consideration. The Committee accepted that the safety characteristics of ibuprofen were well known and that a Schedule 2 classification was appropriate, but considered that the entry should retain a restriction on the maximum total quantity of ibuprofen in the manufacturer's pack, on the grounds that there was potential for poisoning following accidental ingestion by children. At this time the ibuprofen Schedule 2 entry was reworded to explicitly include the limit of 4 grams in total quantity for liquid preparations.

Subsequent considerations of the scheduling of ibuprofen by the NDPSC were related primarily to an exemption from scheduling of small packs of divided preparations with specific requirements for packaging and labelling.

SCHEDULING STATUS

Ibuprofen is currently listed in Schedules 2, 3, 4 and Appendix F. Ibuprofen preparations are also available as unscheduled. The Schedule 2 entry limits liquid ibuprofen for oral use to preparations sold in the manufacturer's original pack containing 4 grams or less of ibuprofen and labelled with a recommended daily dose of 1200 mg or less of ibuprofen.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX requested an increase to the maximum allowed ibuprofen quantity in Schedule 2 liquid preparations from 4 g to 8 g. The application proposed no change to the wording of ibuprofen in relation to solid oral dosing forms. A number of points were made, including:

- Proposed a change in the maximum quantity of ibuprofen included in a 200 mL pack to allow 200 mg/5 mL (40 mg/mL or 4 per cent) to be available as Schedule 2. The recommended maximum daily dose and labelling, including warning statements, would remain unaltered.
- Asserted that the current 4 g restriction on total ibuprofen content was limited for treating an average sized family. Advised that ibuprofen liquid dosing products currently in the Australian market included:
  - Babies 3+ months – 4 per cent suspension (allowing small volumes to be given) with one pack size of 50 mL (i.e. total quantity of 2 g of ibuprofen).
  - Children 1-5 years – 2 per cent suspension, in pack sizes of 100 mL (total quantity 2 g of ibuprofen) and 200 mL (total quantity 4 g of ibuprofen)
  - Children 5-12 years – 4 per cent suspension in a pack size of no more than 100 mL (total quantity 4 g of ibuprofen).
- Noted that the approved dosage of ibuprofen for children aged 6-12 years was 10 mg/kg, tabulated as follows:

Age	Average weight	Maximum daily dose (mg)	Maximum daily dose (ml)	No of days with 100 ml	
				One child	Two Children
5-7 yrs	18-22 kg	660	16.5	6	3
7-9 yrs	22-29 kg	840	21.0	4.8	2.4
9-12 yrs	28-41 kg	1200	30.0	3.3	1.7

- Asserted that there was evidence that the average duration of treating fever, cold / flu symptoms, sore throat or earache in children was 2.8-3.2 days and, since the average Australian family includes 1.6 – 1.9 children, a 100 mL bottle of 4 per cent ibuprofen was inadequate to cover the average duration of treatment required for an average sized family with older children (9-12 years).
- Stated that 46 per cent of children aged 6 years and over had difficulty swallowing a solid dosing form and therefore there was a need for a liquid formulation for children in the older age group of 7 to 12 years.
- Claimed that there were only two analgesic / antipyretic options for treating children with a liquid formulation: ibuprofen and paracetamol. Noted that there was no size restriction on liquid preparations of paracetamol in Schedule 2.
- Ibuprofen has been widely used as an anti-inflammatory / analgesic / antipyretic for almost four decades.
- A recent meta-analysis of 85 studies comparing ibuprofen to paracetamol has shown that ibuprofen was as, or more, efficacious than paracetamol for the treatment of pain and fever in both adult and paediatric patients. There was no significant difference between ibuprofen and paracetamol in adverse event (AE) incidence.
- Unlike paracetamol, ibuprofen had a lower potential for toxic effects at doses up to 200-400 mg/kg. The half-life for overdose was also relatively shorter and averaged from 1.9 to 2.2 hours. This eliminated the need of prolonged observation periods in cases of suspected poisoning.
- Worldwide pharmacovigilance data demonstrated that ibuprofen had a low potential for misuse/abuse or serious adverse events, especially in children.
- Referred to XXXXX showing 814 AEs from 278 case reports. 110 of the 278 reports were from children up to 12 years old. AEs reported were non-serious and resolved spontaneously.
- XXXXX. Overall, the incidence of AE could be rated as very low even if under-reporting occurred.

Evaluation Report

The evaluation report supported the application to increase the maximum pack size of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8 g of ibuprofen. The evaluator stated that although the application requested an increase to 8 g at least, the evaluation focussed on the proposed doubling of the current maximum total quantity and did not consider any greater maximum than 8 g. The evaluator gave the following reasons for the recommendation:

- Ibuprofen had a good safety record relative to other non-steroidal anti-inflammatory drugs (NSAIDs) and relative to aspirin and paracetamol. Ibuprofen had a very low to absent potential for abuse and a low rate of serious effects after overdose. The risk of accidental overdose was low, and the clinical effects of such overdose were usually

mild. Asserted that an increase in pack size was unlikely to increase the likelihood of misuse, poisoning or adverse effects.

- The dosing recommendations for children were based on the recommendation of 10 mg/kg, resulting in adult doses for children with body weights of more than 20 kg. The evaluator stated that a more appropriate dosing recommendation might be 5 – 10 mg/kg, starting with 5 mg/kg and increasing only if required. This would be more consistent with the adult dosing recommendation of 200-400 mg.
- Ibuprofen products have been available for OTC use in Australia since 1989, with no significant safety issues arising over that time. There was considerable OTC marketing experience for the 200 mg unit dose under Schedule 3, Schedule 2 and more recently unscheduled in small pack sizes, and the spontaneous reporting rate of AE has been very low.
- Contended that while the applicant's argument for a public health benefit for a greater maximum quantity (ability to treat two ill older children in the same family from the same pack) was of tenuous relevance, the inconsistency with the solid dosing forms, and the evidence that overdose was infrequent and usually caused no significant medical effects, both supported the request to increase the maximum quantity to 8 g per pack.

Further recommendations related to labelling were made by the evaluator (Members noted that these were regulatory matters for the TGA to consider and were not scheduling issues):

- The delegate may wish to refer the dose recommendations for ibuprofen in children for review by the appropriate body, given the likelihood that many children receiving 10 mg/kg may respond equally well to 5 mg/kg.
- The labelling of the proposed 200 mL container should be amended to reflect any changes in the dosing recommendations and to remove any misleading suggestion that this was a new or more concentrated product rather than merely a larger sized pack of a previously available product.

The evaluation report also raised a number of specific points in response to the application's claims, summarised below:

- Noted that the NDPSC imposed limit of 4 g on maximum quantity in liquid preparations appeared to have related initially to Trans-Tasman harmonization, rather than having been set on scientific grounds.
- Noted that although the minutes of the May 2000 NDPSC meeting indicated that the decision was based on consistency with divided dose formulations, the 4 g limit for the liquid form was considerably lower than for Schedule 2 or 3 packs of oral divided dose forms (maximum quantity per pack is 20 grams, presented as 100 x 200 mg units, or 50 x 400 mg units in Schedule 2 and Schedule 3 respectively).

- Stated that the applicant's argument that pack sizes should accommodate treatment of more than one individual seemed unusual, in that most pack sizes and maximum quantities were designed for short-term treatment of a single individual. Asserted that while there was a case for increased efficiency and convenience for families with two older children who become ill at about the same time with similar symptoms requiring treatment with ibuprofen, it did not appear to be a particularly strong argument.
- In relation to the application's claim regarding the recommended dose in children (solid vs liquid formulations):
  - Asserted that this seemed excessively high given that adults often respond to 200 mg and there was no obvious reason why children should require a larger dose than adults for similar symptoms.
  - Noted that oral solid dosing forms have a recommended dose for children of 200 mg every 6-8 hours (i.e. 5 mg/kg for a 40 kg child).
  - Noted a meta-analysis of paediatric pain in which ibuprofen was given at doses varying between 5 mg and 20 mg/kg. Analysis of the dose-dependency of the outcome (analgesia) did not portray a close relationship since the study using 5 mg/kg had a positive result while the study using 20 mg/kg did not. Noted that unless there was a difference in bioavailability between the solid and liquid dosing forms (which, if present, would usually be expected to be higher for the liquid preparation than for the solid, rather than *vice versa* as the dosing recommendations would suggest), this difference in dose was difficult to justify.
  - Also suggested that based on a 5 mg/kg dosage (sufficient for a therapeutic effect) a 100 mL bottle of 4 per cent ibuprofen would last for the required 3.3 days in a family with two ill children in the older age bracket.
- In relation to the application's claim of inconsistency with the maximum quantity allowed in divided dose preparations, the evaluator made the following comments:
  - Despite the paediatric indication for the liquid formulation, it did not seem reasonable for the total quantity of ibuprofen in the liquid formulation to be so much lower than in the solid dosing forms (maximum of 4 g for the liquid vs 20 g for the Schedule 2 and Schedule 3 products). Asserted that given the dosage recommendations, older children weighing 40 kg or more would therefore receive single doses of 400 mg (i.e. the same as the maximum adult dose).
  - Major concern was inadvertent overdose and whether there was a greater risk associated with the liquid formulation vs solid dosing forms. Stated that pharmacovigilance data XXXXX suggested that accidental overdoses occurred more commonly with the tablet formulation than the capsule or liquid formulations.
  - Noted that based on the number of packs sold during that period, liquid products were slightly over-represented in accidental overdose data (i.e. accounting for about one third of the reports of accidental overdose, but for only about one sixth

of the packs sold). Asserted that the very low incidence of overdose in the context of a very large quantity of sales made these data difficult to interpret, but was also reassuring in that accidental overdose, particularly leading to any significant harm, appeared to be a very rare event.

- Noted that no deaths were reported in Australia, although there were fatal outcomes in the UK database, mainly related to gastrointestinal effects.

· Regarding the inconsistency between paracetamol and ibuprofen in liquid forms, stated that the lack of a maximum quantity for paracetamol appeared anomalous, given its known severe toxicity at relatively low doses. Asserted that this should be addressed as a separate issue. Noted evidence in the submission to support the view that ibuprofen was as efficacious as paracetamol as an analgesic / antipyretic in children, and carried a better safety profile in overdose.

· Noted that in the UK, products containing total quantities of 4 g of ibuprofen in liquid preparations were available as "General Sale" items.

The evaluator also addressed matters listed under s52E, also reflecting the applicant's discussion of these matters, as follows:

(a) Toxicity and safety

· Noted that ibuprofen had a very wide therapeutic index and a potentially fatal dose has not been defined in humans. The poisoning data provided in the submission indicated that ibuprofen was an infrequent cause of hospitalization of children due to poisoning, accounting for about 10 per cent of the total number, compared with 90 per cent for paracetamol.

· Also noted that the Victorian Poisons Information Centre advisesd parents to keep the child at home if the suspected accidental overdose was less than 200 mg/kg. If the total contents of a 200 mL bottle containing 8 g of ibuprofen were consumed by a child, a medical assessment would be required if their body weight was less than 40 kg. The evaluator stated that according to the data, in most cases children did not consume the entire contents of a bottle.

· ADRAC data (2005 – 2010) indicated four accidental exposures (solid dose) in children aged 2-3 years and no deaths in children who had taken ibuprofen, compared with 6 deaths following paracetamol ingestion. US data confirmed the low incidence of accidental ingestion of ibuprofen, and the low frequency of major effects from ingestion of all analgesics.

(b) Risks and benefits

· Noted that the most frequent AEs are gastrointestinal (GI) symptoms and serious GI effects (upper GI bleeding), and that these were less common with ibuprofen than with other NSAIDs. Pharmacovigilance data from the ADRAC database indicated that significant AEs were very rare.

(c) Potential hazards

· Asserted that the major hazard was accidental poisoning, which may be exacerbated by a flavoured liquid presentation. Noted that this risk was minimised by the use of child-resistant closures, the provision of syringes for dose measurement and appropriate label warnings.

(d) Extent and patterns of use

· Noted that XXXXX packs of liquid ibuprofen products for children were sold over a one year period XXXXX. Asserted that ibuprofen was very widely used, and yet had been associated with very few reports of problems.

(e) Dosage and formulation

· The proposed product that would contain 4 per cent ibuprofen in a volume of 200 mL (total quantity of 8 g) was designed for older children but could be used in younger children at the appropriate weight-based dose. Reiterated that the doses provided on the label use the recommended dose of 10 mg/kg, which may be higher than the minimum effective dose in some children. This issue required revisiting, particularly in light of the dose recommendation of 5 mg/kg for solid dosing forms, and a lack of evidence that the liquid form has lower bioavailability than the solid form.

(f) Need for access

· Stated that the applicant pointed out that currently there were only two analgesic/antipyretic options for treating children with a liquid formulation, and these were ibuprofen and paracetamol. Commented that paracetamol was much more toxic in overdose and had a relatively narrow therapeutic index. Notwithstanding this, it was listed in Schedule 2 with no limit to the total quantity present in a container. Argued that the difference between the two drugs was not justifiable. The evaluator recommended that to redress this inconsistency, two options could be considered – either to impose a maximum total quantity limit on paracetamol products, or increase (or remove) the maximum total quantity limit on ibuprofen products.

(g) Potential for misuse/abuse

· Stated that ibuprofen was not a drug of abuse in any dosing form, including liquid formulations or tablets for oral use. There was no likelihood of diversion for illicit use.

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

· Noted that ibuprofen was used for the treatment of inflammation, pain or fever. The liquid formulation was intended for the treatment of children with acute, self-limited

conditions such as toothache, colds and flu, headache and minor sprains and strains. The duration of therapy was estimated to be 3-4 days in most individuals.

In addition, the evaluator summarised the public health considerations as follows:

- There were no particular public health concerns in relation to an increase in quantity of ibuprofen from 4 g to 8 g in liquid formulations. The potential hazards associated with the availability of this product were low, and in particular there was good evidence that ibuprofen taken in overdose rarely lead to significant symptoms or AEs.
- The major public health issue that has arisen during consideration of this application was the inconsistency in dose recommendations for ibuprofen in the liquid formulation vs solid-dose forms.

Applicant's Response to the Evaluation Report

The applicant welcomed the recommendation from the evaluation. The applicant addressed the matter of the dosing recommendation of 10 mg/kg previously approved by the TGA on the bases that a 10 mg/kg dose of ibuprofen provides the following:

- A therapeutic benefit over lower doses in the range 5-10 mg/kg.
- Comparable analgesic efficacy to 15 mg/kg paracetamol.
- Adequate efficacy when given 3 times per day compared with 3-4 times per day. In terms of antipyretic activity, the higher doses produced a longer duration of action.

February 2011 Pre-meeting Submissions

XXXXX supported the proposal to amend the Schedule 2 liquid preparations of ibuprofen to a maximum limit to 8 g. XXXXX also commented that the upper limit must not exceed 8 g.

XXXXX

The submission reiterated the argument from the application regarding the current lack of pack size restriction for paracetamol, and that the liquid ibuprofen pack size was not adequate for an average family with older aged children. The submission also summarised additional matters under 52E as follows:

Risks and benefits

- Ibuprofen was one of the most widely used NSAIDs in Australian children as it had been freely available over the counter since 1998. It was the second in-line therapy after paracetamol. The analgesic and antipyretic efficacy of ibuprofen compared to paracetamol were evaluated in a meta-analysis of 85 studies. The results showed that ibuprofen was as or more efficacious than paracetamol for the treatment of pain and

fever and there were no significant difference between ibuprofen and paracetamol in adverse event incidence.

- When compared to other NSAIDs e.g. ketoprofen, piroxicam, indomethacin, naproxen, sulindac, aspirin and diclofenac, ibuprofen was associated with the lowest relative risk of serious gastrointestinal complications.
- AEs were medically confirmed in 60 children (124 AE) and not medically confirmed in 41 children (59 AEs) in Australia. The medically confirmed AEs in children in decreasing order were skin and subcutaneous disorders; gastrointestinal disorders; general disorders and administration site conditions; psychiatric disorders; and injury, poisoning and procedural complications. The AEs which were not non-medically confirmed were mainly accidental overdoses, followed by skin and subcutaneous disorders; gastrointestinal disorders; and psychiatric disorders. Of the 127 medically confirmed AEs, the gastrointestinal disorders consisted of haematemesis, vomiting, lip oedema, abdominal pain, diarrhoea, gastrointestinal pain, gastrointestinal haemorrhage, tongue oedema, duodenal ulcer perforation, nausea, gastroenteritis, gastritis. Taking into account the number of units sold over this period and under-reporting of AEs, the incidence of gastrointestinal disorders was estimated to be very low.

Toxicity

- Argued that with paracetamol, liver damage was possible in adults who have taken 10 g or more in a single ingestion (or 200 mg/kg for an average adult). The therapeutic dose of paracetamol for adults was 4 g per day. Asserted that poisoning guidelines for ibuprofen suggested that ingestion of more than 400 mg/kg in children may cause adverse symptoms (liver damage). Based on the therapeutic dose of 10 mg/kg, the therapeutic index of ibuprofen was relatively wider than that of paracetamol.
- Reiterated that the half-life for overdose was relatively shorter and averaged from 1.9 to 2.2 hours. This eliminated the need of prolonged observation periods in cases of suspected poisoning.

Dosage and formulation

- Asserted that in order to mitigate the risk of dosing errors, the liquid preparations of ibuprofen for children were specifically labelled to each of the age groups, as previously indicated in the application.
- Also noted that since ibuprofen liquid preparations in Schedule 2 were limited to no more than 4 g of ibuprofen, the pack size for liquid preparations of ibuprofen for children between 5-12 years was limited to 100 mL.

XXXXX

The submission made the following additional comments:

- Increasing the Schedule 2 liquid maximum content to 8 g would facilitate the availability of larger pack sizes of stronger products for use in older age groups, and would mean that the non-prescription availability of ibuprofen would be on an equivalent footing to that for paracetamol. Members noted that while it would allow larger pack sizes it would not broaden the restriction of recommended daily dose i.e. it would not allow 'stronger' products than allowed by current scheduling.
- Paracetamol and ibuprofen were the main non-prescription analgesics used for treating pain and fever in children. Both were available as Schedule 2 products in a range of strengths for paediatric use from infancy to 12 years.
- In general, these medicines were safe and effective when used at their recommended doses, and although paracetamol was generally regarded as the preferred first choice, there were situations where one may be more appropriate than the other.
- A Schedule 2 listing of paediatric analgesics containing paracetamol or ibuprofen provided parents with reliable access to these medicines throughout Australia, many of which have extended trading hours to facilitate after-hours access.
- The quality use of these medicines could be attained with appropriate labelling and packaging supported by assistance from trained pharmacy assistants.
- With paediatric medicine, doses vary significantly according to the age and weight of the child, and children were equally at risk of AEs.
- With the availability of a variety of products with the same brand naming for different age groups, and possibly even different indications (e.g. cold and flu versus analgesic), it was essential that parents or carers of children had access to professional support to ensure they have the right dose for the right medicine for the right condition.
- Ibuprofen liquid preparations registered for the 5-12 year age group were the same strength as that for the 1-5 year age group. Compared this to Schedule 2 paracetamol products which had different strengths available for different age groups.
- Stated that availability of stronger products for older age groups was sensible in that smaller volumes of medicine were given at any one time to a sick child, so adherence was improved, and generally, these products were more cost-effective for consumers to purchase.

May 2000 NDPSC meeting

The NDPSC considered a proposal for the Schedule 2 entry for ibuprofen be amended to include oral liquid preparations containing more than 20 mg/mL of ibuprofen. The NDPSC supported the amendment to the Schedule 2 to include liquid preparations labelled with a recommended daily dose for ibuprofen of 1200 mg or less of ibuprofen. However, it was considered that the entry should retain the restriction on the maximum quantity of ibuprofen in the manufacturer's pack inherent in the current entry. It was considered undesirable to allow the entry to include large pack sizes of a concentrated liquid because of the potential for poisoning following accidental ingestion by children.

The NDPSC decision was based on:

- The safety profile of ibuprofen and that Schedule 2 was appropriate when used in analgesic dose for minor and temporary ailments for short periods.
- Consistency with divided dose formulations.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members noted that the previously imposed 4 g total limit of ibuprofen in liquid preparations in Schedule 2 was a result of Trans-Tasman harmonisation rather than based on safety concerns. A Member stated that data available on ibuprofen showed a good safety record, and the incidence and severity of adverse events was low in comparison with paracetamol.

A Member asserted that the argument of the inadequacy of current pack sizes for treating more than one individual did not justify an increase in pack size in and of itself. Another Member asserted that an increase in pack size would be comparable with divided preparations of ibuprofen currently captured by Schedule 2. The Member argued that consistency in the amount of ibuprofen for pack sizes in Schedule 2 would be appropriate. Another Member stated that an increase to 8 g would also be consistent with the scheduling of liquid preparations for comparable actives.

A Member raised concerns that a larger bottle containing 8 g ibuprofen could imply a "stronger" product and may be a cause of confusion for parents when dispensing to their children. A Member further stated that NSW Poison Centres report numerous calls related to liquid ibuprofen of which 30 per cent are due to errors in use in children. However, it was noted that issues regarding appropriate dosage are addressed by the products' labelling.

Members generally agreed that it would be appropriate to increase the maximum amount of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8 g.

Implementation date

Members considered the implementation date for the recommended rescheduling. The Committee acknowledged that an implementation period of less than 6 months may provide certain companies with a competitive advantage. A Member noted that this was frequently the case where a substance was rescheduled. It was also noted that a 6 month period was roughly equivalent to processes under the previous scheduling arrangements and there was no reason for a delay in implementation. Members agreed to recommend to the delegate an implementation date of no more than 6 months after the delegate's final decision.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (d) dosage and packaging.

DELEGATE'S INTERIM DECISION

The delegate decided to increase the maximum allowable amount of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8 g. The delegate also decided on an implementation date of 1 September 2011 (three months following publication of the delegate's final decision in June 2011).

SUBMISSIONS ON INTERIM DECISION

Following publication of delegate's interim decision a further submission was received from XXXXX. The submission supported the delegate's interim decision to amend the ibuprofen Schedule 2 entry to increase liquid preparations containing ibuprofen from 4 g to 8 g. The submission also supported the delegate's implementation date of 1 September 2011.

The submission reiterated many points from the February 2011 pre-meeting submissions::

- Toxicity and safety: the long history of safe ibuprofen use in Australia as demonstrated by pharmacovigilence data indicating low potential for abuse and a low rate of serious adverse events following overdose. Reasserted that ibuprofen had a wide therapeutic index and had a lower potential for toxic effects at doses up to 400 mg/kg.
- Risks: noted that gastrointestinal symptoms and serious gastrointestinal effects were the most frequently reported adverse events and reasserted that these adverse events were less common with ibuprofen than with other NSAIDs. Reasserted that ibuprofen accidental poisoning was unlikely to increase with the increased maximum quantity supported in the proposed amendment and was minimised by child resistant closures, clear closing instructions, provision of measuring devices and label warnings.
- Other considerations: again compared the amount of liquid ibuprofen available as Schedule 2 with solid dosing forms. Reiterated the current lack of pack size restrictions for liquid paracetamol in Schedule 2.

DELEGATE'S FINAL DECISION

The delegate confirmed that the maximum allowable amount of ibuprofen in liquid preparations in Schedule 2 be increased from 4 g to 8 g. The delegate also confirmed an implementation date of 1 September 2011.

Schedule 2 – Amendment

IBUPROFEN – Amend entry to read:

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200mg or less of ibuprofen:

(a) in liquid preparations when sold in the manufacturer's original pack containing 8 grams or less of ibuprofen; or

(b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:

(i) as the only therapeutically active constituent other than an effervescent agent;

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

(iii) in a primary pack containing not more than 25 dosage units;

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

(v) compliant with the requirements of the *Required Advisory Statements for Medicine Labels.*

2.1.4 IBUPROFEN COMBINED WITH PARACETAMOL

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of ibuprofen combined with paracetamol and decided to seek advice from the ACMS on the following:

Paracetamol + ibuprofen combination – consideration for a higher schedule. Currently in Schedule 2.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that combination ibuprofen+paracetamol preparations currently captured by Schedule 2 (up to 200 mg ibuprofen and 500 mg paracetamol) be included in Schedule 3 in packs of 30 dosage units or less. The Committee recommended that combination ibuprofen+paracetamol in packs of more than 30 dosage units be captured by Schedule 4.

The Committee recommended an implementation date of 1 September 2011 (three months following delegate's final decision).

BACKGROUND

Ibuprofen

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

Ibuprofen was first included in Schedule 4 in February 1973. In October 2003, the NDPSC agreed to exempt from scheduling certain divided preparations of ibuprofen:≤ 200 mg in packs of 25 or less when compliant with label requirements including a recommended maximum daily dose of 1200 mg.

In February 2006, the NDPSC decided to list ≤ 400 mg ibuprofen in packs of ≤ 50 units, when labelled not for the treatment of children less than 12 years, in Schedule 3.

Paracetamol

Paracetamol is a p-aminophenol derivative that inhibits analgesic and antipyretic effects and weak anti-inflammatory activity. Paracetamol is used for the relief of mild to moderate pain.

Ibuprofen combined with paracetamol

In June 2010 the NDPSC considered the scheduling of a combination of ibuprofen and paracetamol and agreed that the current scheduling remained appropriate – Schedule 2 for combinations of up to 200 mg ibuprofen+500 mg paracetamol in packs of up to 100 dosage units. The NDPSC's June 2010 discussion is summarised below under the 'Submissions' heading.

SCHEDULING STATUS

The Schedule 2 ibuprofen entry captures oral preparations when labelled with a recommended daily dose of≤1200 mg ibuprofen in divided preparations with ≤ 200 mg of ibuprofen in packs of ≤ 100 (except when present as the only therapeutically active constituent, where it becomes unscheduled).

Paracetamol preparations containing ≤ 500 mg of paracetamol as the only therapeutically active constituent (other than phenylephrine, effervescent agents or guaiphenesin) in packs of ≤ 25 are exempt from scheduling (when compliant with labelling, packaging and age restrictions). However, these preparations are captured by Schedule 2 when combined with another therapeutic active such as ibuprofen.

INITIAL SUBMISSIONS

Applicant's Submission

A delegate referred a proposal from the TGA Advisory Committee on Non-prescription Medicines (ACNM) to reconsider the scheduling of a combination of ibuprofen and paracetamol (ibuprofen+ paracetamol). Specifically, the ACNM recommended a consideration of Schedule 3 or higher for a combination of up to 200 mg ibuprofen and up to 500 mg paracetamol (200 mg/500 mg – the current limits of the Schedule 2 entries). XXXXX. The submission addressed a number of points, summarised below:

- XXXXX.
- Asserted that based on safety and efficacy data a maximum Schedule 3 pack size of less than 48 units should be considered for a 200 mg/500 mg combination. XXXXX. Therefore a pack containing 48 tablets would provide XXXXX supply at the maximum recommended dose, and could encourage excessive and inappropriate use.
- Raised concerns regarding the effects of ibuprofen on metabolism of paracetamol, the effects of the combination on gastrointestinal toxicity, and the absence of acute and repeat dose oral toxicity studies, genotoxicity studies and reproductive toxicity studies on the ibuprofen+paracetamol combination.
- Raised concerns about the reduction in haemoglobin associated with the 200 mg/500 mg combination. Specifically, noted that use of this combination, in preference to single active ibuprofen 400 mg or paracetamol 1000 mg, would not be justifiable in people aged 65 years and over for periods of 10 days or longer, as greater reductions in haemoglobin were seen in this age group. Noted that use of this combination would be contraindicated in people aged 65 years and over.
- XXXXX. Raised concerns that consumers might use the combination for longer periods, regardless of label warnings.
- Asserted that there was an extensive list of contraindications to the use of ibuprofen+paracetamol, including people with allergies to anti-inflammatory

medicines, people with a stomach ulcer or other stomach disorders, use in pregnancy, people with asthma, heart failure, impaired kidney or liver function or aged over 65 or under 12 years of age. Asserted that the list of precautions and contra-indications was inconsistent with the safety profile of medicines available for self-selection by consumers, and that pharmacist intervention at least was required to assist consumers with safe use of the combination.

- XXXXX.
- Raised concerns that consumers may not read or understand all the information on a label and a Schedule 3 entry would ensure pharmacist advice at the point of sale. Members noted that this appeared to be the ACNM's key reason for seeking up scheduling (i.e. while pack size and indication issues could be dealt with through the product approval process, consumer compliance concerns may need to be mitigated by access restrictions through a higher scheduling classification).

Members noted that in September 2010 the UK's Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorisation for a 200 mg/500 mg combination. The therapeutic indication was for temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. It was classified as a P (pharmacy only) product, for short-term use only, i.e. 3 days with a maximum of six tablets in 24 hours. Longer periods of treatment required consultation with a doctor. Available pack sizes ranged from 4 to 32 tablets.

June 2010 NDPSC consideration

Members noted the following from the June 2010 NDPSC discussion:

- XXXXX.
- A Member felt some concern about this new combination given the lack of Australian experience and suggested that perhaps some initial access restrictions, such as through a Schedule 3 listing, might be appropriate. Several other Members responded, however, that the individual actives had a long history of use in Australia with well known risk profiles and that there was little, if any, evidence that the combination would behave any differently. A Member also noted that there was nothing currently to stop consumers from concurrent use of single active paracetamol and ibuprofen products.
- Several Members asserted that this matter appeared to be an issue best addressed by the regulator, particularly with regard to the disputed efficacy. There appeared to be little data on risks from use of ibuprofen+paracetamol over and above those expected for single active paracetamol and ibuprofen. The NDPSC generally agreed that no strong argument had been presented for changing the current scheduling.
- The NDPSC did note, however, that it was possible that more robust evidence of additional risk could come to light through any application for product approval with

the TGA. The Members recommended that the regulator be alerted to the possible need to refer this combination for scheduling should such evidence emerge.

February 2011 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX.

XXXXX requested that ibuprofen+paracetamol in small pack sizes of 30 tablets or 48 tablets should remain in Schedule 2. XXXXX also supported the inclusion of ibuprofen+paracetamol in smaller pack size in Schedule 2 and further recommended that larger pack sizes be included in Schedule 3. XXXXX recommended that the combination should remain in Schedule 2.

XXXXX

XXXXX.

The submission asserted that ibuprofen+paracetamol combinations in small packs containing 30 tablets would be appropriate for a Schedule 2 listing. Did not support an exemption from scheduling for ibuprofen+paracetamol combinations. The submission raised a number of points specifically in relation to a 150 mg/500 mg combination, which were summarised below:

- The clinical safety of both drugs was well described in multiple publications and regulatory reviews. The prime risks for paracetamol were liver injury in overdose situations but with higher risks in patients with alcohol abuse and malnutrition.
- Ibuprofen was associated with risks of triggering gastro intestinal bleeding and thromboembolic events, however had an extended safety record as an OTC drug over decades, suggesting it had a lower risk of inducing gastrointestinal bleeding in comparison to other drugs from the same class. Claimed that a European Medicines Agency epidemiological evaluation on the risks of thromboembolic events suggested that the OTC approved daily dose of ibuprofen showed no higher risks than placebo.
- The combination showed statistically superior efficacy for the combination over either paracetamol or ibuprofen, each administered at their approved OTC maximum daily doses.
- XXXXX.
- Claimed that, as the two drugs did not share metabolic pathways, their co-administration was not accompanied by any increase in adverse outcomes.
- Noted the risks that may lead to overdose, including higher than approved daily doses, confusion from labelling issues and situations where additional analgesia was needed leading to the use of another paracetamol based analgesic. Stated that this risk may be limited by restrictions in the availability of pack sizes (proposed dosage of one to two tablets up to four times a day for a 150 mg/500 mg combination would not

reach the maximum approved daily dose of paracetamol). Members noted that the submission did not indicate if such restrictions should be imposed through the product approval process or scheduling.

- Claimed the ibuprofen+paracetamol combination offered superior efficacy to either paracetamol or ibuprofen when combined with codeine and could be used to displace existing use of opioid combination analgesics. Provided detailed information on the hazards and risks associated with the use of opioid drugs alone or in combination.

XXXXX

Stated that a 200 mg/500 mg ibuprofen+paracetamol combination in packs of up to 48 tablets should remain as Schedule 2. The submission made no comment regarding scheduling of larger pack sizes. The pre-meeting submission also made a number of points, which have been summarised below:

- Noted that since the June 2010 NDPSC decision a 200 mg/500 mg product had been registered in the UK as a P licensed medicine (Pharmacy-Only-Medicine). Members noted that in the UK, a P licensed medicine was equivalent to Schedule 3 in Australia.
- The combination was indicated for the short-term relief of pain and fever and was not intended for treatment of a chronic condition.
- Since the 2010 implementation of the rescheduling of all OTC combination analgesics containing codeine (CACC) consumers have a limited choice for pain relief. Noted that this situation may lead consumers to increase their dose of analgesics (such as paracetamol or ibuprofen alone) leading to increased adverse effects.
- Noted the long history of use of both actives for the treatment of minor ailments. Asserted that these ailments could be easily recognised and managed by the consumer and were unlikely to be confused with more serious conditions.
- The combination provided an alternate safe and more effective pain relief than either paracetamol or ibuprofen as the only active ingredient. Maintained that Schedule 2 was appropriate as this would ensure that a pharmacist was available to provide advice and education to consumers on responsible use of the product.
- Both ibuprofen and paracetamol have well-documented safety profiles and there was a low and well characterised incidence of adverse effects for both substances which was shared by the combination at the proposed dose.
- Noted that at the proposed maximum daily dose for the 200 mg/500 mg combination there was a reduction in the daily amount of both ibuprofen and paracetamol ingested compared to the maximum daily dose of the individual components, thus minimising the risk of unwanted side effects.
- Noted data suggesting that there were no pharmacokinetic interactions between ibuprofen and paracetamol that would give rise to safety concerns. Noted data

suggesting that concomitant use of ibuprofen and paracetamol did not increase risk of the various safety outcomes examined over use of paracetamol or ibuprofen alone.

· Noted that in NZ a 150 mg/500 mg combination had been scheduled for General Sale in pack sizes of 8 and 16 tablets and as Pharmacy only for pack sizes of 50 and 100 tablets.

XXXXX

Also asserted that the appropriate schedule for paracetamol and ibuprofen combination products was Schedule 2 for smaller pack and Schedule 3 for larger pack sizes. The submission did not suggest a Schedule 2 cut-off for pack size. The submission also made a number of points summarised below:

· Reiterated previously mentioned comments regarding the 150 mg/500 mg combination's efficacy and individual substances' safety profile, including:

  - Patients with arthritis commonly take paracetamol with one of the prescription NSAIDs and there would be concern about consumers taking excessive quantities of NSAIDs.
  - Concerned that industry would market this combination as a substitute for the combination analgesics containing codeine.

· Noted that a combination product carried a wider spectrum of precautions and potential side effects or interactions.

· Asserted that the current Schedule 2 allowance of a maximum pack size of 100 dosage units was excessive, noting the product's recommended maximum of 6 dosage units per day and three days supply, as well as the availability of other products containing the same actives and the potential for excess intake.

XXXXX

Supported the inclusion of small pack sizes of a fixed dose ibuprofen+paracetamol product in Schedule 2 with larger pack sizes included in Schedule 3. The submission did not suggest a Schedule 2 cut-off for pack size. The submission also made a number of points, summarised below:

· Paracetamol and ibuprofen were commonly prescribed together in clinical practice, however compliance could be poor with asynchronous dosing.

· Raised comments regarding the combination's efficacy, safety and associated adverse effects, including:

  - Paracetamol has a low incidence of AEs when compared to other drugs.
  - The more common AEs of ibuprofen relate to upper GI effects. Other common AEs include raised liver enzymes, diarrhoea, headache, dizziness, salt and fluid retention and hypertension.

- Hepatotoxicity was the greatest risk following paracetamol over dosage.

· Stated that the availability of a combination product provided consumers and clinicians with an effective- and cost-effective product that simplified the dosage schedule for both active ingredients. Also noted that the availability of a combination analgesic in Schedule 2 may assist in reducing consumers' reliance on analgesics combined with codeine.

· Asserted that although having relatively safe profiles, the relative risk of these medicines, particularly in combination, warranted consumer access to advice and support from a pharmacist or other appropriate health professional.

· Asserted that small packs met the factors for a Schedule 2 listing, where the quality use of the product could generally be achieved by labelling and packaging and information provided by a pharmacy assistant, with the pharmacist available if required. Noted the need for appropriate training of pharmacy assistants to ensure they could adequately triage patients and refer to the pharmacist when appropriate.

· Asserted that the availability of small packs of an ibuprofen/paracetamol combination product in Schedule 2 could also have a positive impact on pharmacy workflow by having alternative therapies available without the need to always consult a pharmacist.

· Asserted that large packs met the factors for a Schedule 3 listing, specifically noting:

- *Patients requiring ongoing treatment benefit from the intervention of a pharmacist to assess the situation and ensure there were no complications that would warrant review by another health practitioner.*

- *Provided an opportunity for the pharmacist to ensure effective treatment, appropriate use and that the patient is not doubling up on other paracetamol based products or suffering adverse effects from ibuprofen use.*

XXXXX

· Supported maintaining the Schedule 2 listing of the combination. Claimed that concomitant use of ibuprofen and paracetamol did not increase safety risk.

· Acknowledged that combination products may contribute to unintentional overdose (with consumers taking multiple products containing the same active). Asserted that this issue could be adequately dealt with through product labelling and would be best addressed by the regulator.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members discussed the safety profiles of the two substances. A Member queried the apparent lack of pharmacokinetic interaction between ibuprofen and paracetamol when coadministered. Other Members asserted that the available safety data related to co-administration of single actives and may not be indicative of the usage of a fixed

combination. A Member also noted the potential drop of haemoglobin associated with the use of ibuprofen+paracetamol and asserted that risks surrounding the potential toxicity of the combination may warrant concern. Another Member asserted that the ibuprofen+paracetamol combination was safe when appropriately administered.

Members also discussed the efficacy of ibuprofen+paracetamol. A Member stated that due to the substances' different mechanisms of action there would be little additional efficacy of the combination compared to other analgesics. Another Member asserted, however, that there was some clinical data which reported some increase in efficacy of ibuprofen+paracetamol, indicating a potential clinical advantage.

A Member argued that certain combination products, such as cough and cold medicines, were currently available as Schedule 2. However, another Member asserted that these products were used for the relief of short-term symptoms, whereas combination products used for the treatment of pain have greater potential for long-term use. The Member stated that availability of these products as Schedule 2 increased the risk of consumers buying multiple packs without seeking pharmacist advice.

Members raised concerns regarding consumers' understanding of products containing more than one active. A Member asserted that patients may not perceive that they were taking two medications in one tablet. The Member stated that accidental "double-dosing" was a significant risk associated with combination products due to the use of more than one product containing paracetamol and/or ibuprofen. The Member also stated that these risks would be amplified if no pharmacist advice was provided at the point of sale. Another Member asserted that due to this potential for confusion, even a Schedule 4 classification for fixed combination products may not ensure that consumers receive the necessary advice for the medicine's safe use. The Member argued that at the very least, all combination products should be listed in Schedule 3. Other Members agreed that the risks associated with combination products were greater than with products containing single actives, however contended that the schedule of these combinations needs to be addressed on a case-by-case basis.

Members generally agreed that ibuprofen+paracetamol combination products should be restricted to Schedule 3 at least, noting that in the future (following additional marketing experience) an application for down-scheduling of this combination could be considered. Members also noted that the Schedule 3 listing would preclude the advertising of these products and agreed that this was appropriate at this time.

Larger pack sizes

Members discussed the need to limit larger pack sizes of ibuprofen+paracetamol to Schedule 4. A Member queried whether it would be more appropriate for the TGA registration processes to address the issue of larger pack sizes. Other Members generally agreed that in this instance a scheduling cut-off to Schedule 4 for larger pack sizes would be warranted to minimise the risks associated with inappropriate use of the combination.

Members discussed the risks and benefits of different pack sizes ranging from 50 to 25 dosage units. Members noted that the current Schedule 4 pack size cut-offs for single-active ibuprofen and paracetamol were 50 and 100 dosage units, respectively. A Member asserted that a cut-off of 50 units may be beneficial as these packs could be used for more than one course of treatment. Members noted that depending on the concentration of ibuprofen/paracetamol in the combination the recommended treatment dosage would differ. Members noted that in the UK the current pack size available as a Pharmacy medicine (equivalent to Schedule 3) was a maximum of 32 dosage units. A Member asserted that due to the amount of ibuprofen+paracetamol contained in each pack, pack sizes of more than 30 dosage units were associated with greater risks to the consumer.

Members generally agreed that, on-balance, ibuprofen+paracetamol in packs of 30 dosage units or less should be included in Schedule 3 and larger packs should be captured by Schedule 4.

Implementation date

Members discussed an appropriate implementation date. It was noted that there was currently no registered product in Australia containing a fixed ibuprofen+paracetamol combination and agreed that an early implementation date would be appropriate. Members agreed to recommend to the delegate an implementation date of 1 September 2011 (three months following the delegate's anticipated final decision).

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose of use; (c) toxicity; and (d) dosage and formulation.

DELEGATE'S INTERIM DECISION

The delegate decided that combination ibuprofen+paracetamol preparations currently captured by Schedule 2 (up to 200 mg ibuprofen and 500 mg paracetamol) are to be rescheduled to Schedule 3 when in packs of 30 dosage units or less. The delegate also decided that combination ibuprofen+paracetamol in packs of more than 30 dosage units are to be captured by Schedule 4.

The delegate decided on an implementation date of 1 September 2011 (three months following publication of the delegate's final decision in June 2011).

SUBMISSIONS ON INTERIM DECISION

A further submission received from XXXXX opposed the interim decision and asserted that the current scheduling of ibuprofen+paracetamol when in combination preparations of up to 200 mg ibuprofen and 500 mg paracetamol should remain as Schedule 2 in pack sizes of up to 48 dosage units.

The delegate noted that although the submission assumed that the matter would be further discussed at the June 2011 ACMS meeting, XXXXX had since been advised that this matter was expected to be finalised following consideration of the submission by the delegate and not re-referred to the June 2011 ACMS meeting.

The submission also made several points, summarised below:

- Noted that in September 2010 in the UK a 200 mg/500 mg product had been approved for registration as a Pharmacy-Only Medicine. Noted that this same combination was also approved in Poland in December 2010. XXXXX. Referred to the previously submitted UK MHRA report.
- Reiterated previously made points regarding a lack of available evidence regarding effects of ibuprofen on paracetamol metabolism and the two substances' clinical safety, bioavailability and pharmacokinetic profiles.
- Stated that the proposed posology was dose-sparing XXXXX. Noted that the reduction in haemoglobin effects observed in people over 65 were seen following 10 days of use with a XXXXX posology. Asserted that the product would be contraindicated for this population and addressed by labelling.
- Asserted that there was no information to suggest that consumers would take the combination for longer than its recommended duration XXXXX.
- XXXXX.
- Asserted that user testing of labelling and consumer testing of packaging readability XXXXX demonstrated that consumers were clear that the product contained two actives. XXXXX.
- Reiterated previously mentioned overall benefits of the proposed combination including a possible alternative to OTC codeine combination products, the combination's efficacy, the dose-sparing posology, the simplification of treatment compared to single-active treatments taken concomitantly.

The submission also commented on matters under s52E, summarised below:

- Reasserted previously made points regarding the risks and benefits of the combination, namely the long availability of the single actives; the minor nature of the ailments indicated for treatment; the combination's efficacy; use of the combination as an alternative to single active presentations; the availability of

pharmacist advice for Schedule 2 products and the actives' safety profiles at the proposed dose.

- Asserted that results from a retrospective study suggested that concomitant use of ibuprofen and paracetamol did not increase risk of safety outcomes examined over use of paracetamol or ibuprofen alone.
- Reiterated that the combination was not intended for treatment of a chronic condition.
- Reasserted that consumers were used to self-medicating with paracetamol and ibuprofen containing analgesics and familiar with the contra-indications and pack warnings. Stated that combination packaging and labelling utilising the same warnings and contra-indications would support this familiarity.
- Reiterated the potential for unintentional overdose due to consumer confusion regarding the constituents of the combination. Stated that in this respect the 200 mg/500 mg combination was no different from any other combination of simple analgesics. Asserted that this risk could be mitigated by labelling and provision of educational and promotional material to both pharmacists and pharmacy assistants. Asserted that labelling would be consistent with the TGA's labelling guidelines.
- Asserted that there was no evidence that either paracetamol or ibuprofen was associated with dependency, abuse or illicit use as individual actives and was not expected to produce dependency as a combination.
- Reiterated the availability of ibuprofen/paracetamol combinations in NZ.

DELEGATE'S FINAL DISCUSSION

The delegate considered the only submission received in response to the interim decision and noted that it reiterated many points which were previously raised in pre-meeting submissions which were considered as part of the ACMS's and delegate's interim discussions.

The delegate again noted ACMS Members' concerns in relation to combination products in general and the ibuprofen+paracetamol combination specifically. The delegate reiterated concerns regarding the number of contraindications and precautions and whether consumers would be able to interpret these appropriately without a requirement for pharmacist advice. The delegate also reiterated concerns regarding gastro-intestinal, renal and other adverse effects related to the potential interactions of ibuprofen and paracetamol. The delegate further reiterated concerns regarding the potential for paracetamol overdose.

The delegate reasserted that at this time there a lack of toxicity and clinical safety data for the combination. The delegate noted the XXXXX data provided in the submission and asserted that at this time there was insufficient meaningful post-marketing data to ensure safe use without the need to consult with a pharmacist or GP.

The delegate agreed that the interim decision was appropriate and that combination ibuprofen+ paracetamol preparations up to 200 mg/500 mg should be captured by Schedule 3 in packs of up to 30 dosage units, with larger pack sizes captured by Schedule 4.

DELEGATE'S FINAL DECISION

The delegate decided that combination ibuprofen+paracetamol preparations currently captured by Schedule 2 (up to 200 mg ibuprofen and 500 mg paracetamol) are to be rescheduled to Schedule 3 when in packs of 30 dosage units or less. The delegate also decided that combination ibuprofen+paracetamol in packs of more than 30 dosage units are to be captured by Schedule 4.

The delegate decided on an implementation date of 1 September 2011 (three months following publication of the delegate's final decision in June 2011).

Schedule 3 – New Entry

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less.

Schedule 4 – Amendment

PARACETAMOL – Amend entry to read:

PARACETAMOL:

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

(b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;

(c) in slow release tablets or capsules containing more than 665 mg of paracetamol;

(d) in non-slow release tablets or capsules containing more than 500 mg of paracetamol;

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

(f) for injection.

2.2. PROPOSED CHANGES TO PART 5 OF THE SUSMP (THE APPENDICES)

2.2.1 ASENAPINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of asenapine and decided to seek advice from the ACMS on the following:

Asenapine – proposal to include in Appendix K.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that asenapine be included in Appendix K. The Committee also recommended an implementation date of 1 September 2011 (three months following delegate's final decision).

BACKGROUND

Asenapine is a novel atypical antipsychotic medication. It has been shown to have activity on dopamine (D)-2 and serotonin (5-HT)-2A receptors as well as on 5-HT1A, 5-HT1B, 5-HT2C, 5-HT6, 5-HT7, D3 and alpha-2 adrenergic receptors. Asenapine has highest affinity for blocking serotonin receptors, followed by dopamine and alpha-adrenergic receptors with minimal affinity for muscarinic receptors.

In December 2010, a delegate considered an application to register asenapine and decided that a Schedule 4 entry was appropriate. The delegate also noted data indicating sedation effects associated with asenapine and decided to refer a proposed Appendix K entry for advice from the Advisory Committee on Medicines Scheduling.

SCHEDULING STATUS

Asenapine is listed in Schedule 4.

INITIAL SUBMISSIONS

A pharmacology evaluation was undertaken as part of the TGA registration consideration. The matter was also referred for advice to the Advisory Committee for Prescription Medicines (ACPM). XXXXX. In relation to the scheduling proposal under consideration, the TGA provided the following information:

- The most frequently reported adverse events associated with asenapine were somnolence (11 per cent), weight increase (7.7 per cent), sedation (7.5 per cent), akathisia (6.7 per cent), Parkinsonism (3.5 per cent) and oral hypoaesthesia (3.3 per cent).

- Asenapine was also associated with dizziness and postural dizziness with an incidence of 18.8 per cent and 8.1 per cent respectively.
- The incidence of syncope was 0.4 per cent, similar to that of olanzapine (listed in Appendix K, also associated with other sedation effects).

EXPERT ADVISORY COMMITTEE DISCUSSION

Members noted the incidence of somnolence and dizziness associated with the use of asenapine. A Member also stated that asenapine is currently marketed in the US, where the product information contains similar sedation warnings. Members also noted that substances with similar effects were also currently listed in Appendix K.

Members noted that an Appendix K listing would require a label detailing a sedation warning and advising against the use of machinery or consumption of alcohol. A Member noted that the incidence of somnolence appeared to be dose-related and there was less evidence of an interaction with alcohol. However, another Member asserted that this need not be a major concern as an Appendix K listing indicated a requirement for a warning label; it did not constitute a prohibition label.

Members agreed that an Appendix K listing would be appropriate for asenapine.

Implementation date

Members noted that the delegate's final decision associated with this matter was expected to be published in June 2011. Members generally agreed that there was no need for a delayed implementation date and recommended an implementation date of 1 September 2011 (three months following the delegate's final decision).

DELEGATE'S DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of use; and (d) labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include asenapine in Appendix K. The delegate decided on an implementation date of 1 September 2011 (three months following publication of the delegate's final decision in June 2011).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that asenapine be included in Appendix K. The delegate also confirmed an implementation date of 1 September 2011.

Appendix K – New entry

ASENAPINE

2.2.2 PANTOPRAZOLE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of pantoprazole and decided to seek advice from the ACMS on the following:

Pantoprazole – proposal to create a new entry for pantoprazole in Appendix H.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current scheduling of pantoprazole remained appropriate i.e. no Appendix H listing.

BACKGROUND

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

Pantoprazole was first included in Schedule 4 in February 1995.

In June 2005 the NDPSC 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 (an initial deferred implementation of 1 May 2006 was subsequently further delayed to 1 May 2008, to allow time for the preparation of pharmacist/consumer education materials to support the rescheduling). Also in June 2005, an Appendix H listing was not supported as the NDPSC felt there was insufficient information at the time to allow direct-to-consumer advertising. The NDPSC agreed that it would not consider an Appendix H listing until patterns of use of pantoprazole as a Schedule 3 medicine had been established.

In February 2009 the NDPSC again rejected a proposal to include pantoprazole in Appendix H. The NDPSC 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.

In February 2010 the NDPSC yet again rejected a proposal to include pantoprazole in Appendix H. The NDPSC 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, and concluded that this was not the case for pantoprazole. The NDPSC's February 2010 discussions are summarised below in the "Submissions" section.

Recent considerations of other PPIs – rabeprazole, lansoprazole and omeprazole

In June 2009 rabeprazole (with pack size and indication restrictions similar to those for pantoprazole) was downscheduled to Schedule 3. However, a simultaneous request for Appendix H listing was rejected for the same reasons as for pantoprazole in February 2009.

In February 2010 two PPIs, lansoprazole and omeprazole, were scheduled similarly to pantoprazole and rabeprazole to harmonise with New Zealand. In both cases it was agreed that a consistent approach for all PPIs should be undertaken in relation to Appendix H listing i.e. these PPIs were not included in Appendix H.

In June 2010 the NDPSC again rejected a proposal to include rabeprazole in Appendix H. The NDPSC generally agreed that an Appendix H listing was not appropriate at this time and that it would be beneficial for pharmacists to first become accustomed to having rabeprazole available as a Schedule 3 medicine.

Members noted that another request to include rabeprazole in Appendix H has been received and the delegate had referred the matter for advice to the June 2011 meeting of the ACMS.

SCHEDULING STATUS

Pantoprazole is listed in Schedule 3 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. All other presentations of pantoprazole are captured by Schedule 4.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX requested inclusion of pantoprazole 20 mg in Appendix H. No other change to the scheduling of pantoprazole was proposed. The applicant indicated that this new

application has been in part prompted by concern that the February 2010 NDPSC decision may have been based on erroneous statements made at the meeting.

In summary, the applicant's rationale for the proposal was:

Summary of arguments supporting the current Schedule 3 entry (not currently in question)

- All PPIs have similar efficacy and safety profiles, although there are some differences in relation to their potential to interact with other drugs. PPIs are recognised by gastroenterologists to be the most effective treatment for patients with repeated heartburn due to GORD.
- Pantoprazole is an established chemical entity (first approved for marketing in 1994) for the treatment of acid related gastrointestinal disorders. It is approved in over 90 countries as a prescription medicine, and extensive data are available to support its favourable safety profile. It is available as an OTC medicine in 32 countries, and has been included in Schedule 3 in Australia since mid-2008. A Schedule 3 product was launched in Australia in October 2008.
- The pantoprazole Schedule 3 indication was for heartburn and other symptoms of GORD. The applicant argued that this was consistent with the registered indication, and that it represented a common symptom in the Australian community.
- It was further argued that symptoms of reflux have been safely managed by OTC medications for decades.
- Much of the application consisted of further data, including safety up-date data and clinical trial data relating to the safety and wide therapeutic index of pantoprazole, including its OTC use in Sweden.

Summary of arguments specifically supporting inclusion in Appendix H

- The applicant asserted that pantoprazole had an excellent risk/benefit profile when supplied with pharmacist advice in the OTC setting.
- Advised that XXXXX devoted resources to developing and disseminating a pharmacy training program for the product, with the aim of ensuring that pharmacists were adequately equipped to manage GORD symptoms in patients approaching them. The applicant claimed that these materials have been designed from the perspective of quality use of medicines, and will aid in determining whether the product was a suitable treatment for an individual consumer, as well as facilitating early identification of atypical symptoms that warrant referral to medical attention.
- Argued that advertising would encourage more frequent heartburn sufferers to consult a pharmacist for advice, thus allowing pharmacists to triage consumers and direct them to the most appropriate course of action (which may include supply of PPI, or another medication, or referral for medical advice). This promoted a better use of the professional expertise of pharmacists, and would benefit patients who were self-medicating with less effective remedies, both in terms of improved efficacy due to

PPI use, and also in terms of identification of those with 'red flag' symptoms who should be attending their doctor for further assessment of potential underlying conditions.

· The proposed advertising would not result in the advertising of goods for an indication other than those included in the ARTG, nor result in a change of the purpose for which the product was to be used, nor change the level of involvement of the pharmacist in the supply of the product.

Applicant's Response to February 2010 NDPSC's consideration

· In response to the NDPSC's February 2010 conclusion that the "advertising of pantoprazole would potentially impair the ability of pharmacists to adequately carry out their professional responsibilities" the applicant argued that it was not clear from the record of reasons whether this was based on a proposal that pharmacists would be unable to cope with the number of heartburn sufferers who may present themselves to the pharmacy in response to advertising, or that they would be unable to deal appropriately with those presenting.

  - The evaluator noted that the applicant had not addressed the issue of the potential increase in workload, although support for the proposal from the XXXXX would suggest that the pharmacy profession itself does not have this concern.

  - In relation to the capability of pharmacists to deal appropriately with those presenting themselves for advice, the application provided a published Australian audit of pharmacy practice, which the evaluator agreed demonstrated that pharmacists were able to determine which customers had frequent heartburn, appropriately recommend treatment, and appropriately identify the presence of 'red flag' symptoms and refer customers with severe symptoms to their general medical practitioners.

Evaluation Report

Recommendation

The evaluator supported the proposal to list pantoprazole in Appendix H. Members noted that the February 2010 evaluation report also recommended approval of an Appendix H listing, however this was not supported at the time by the NDPSC.

The key reasons for the evaluator's recommendation are summarised below:

· Asserted that by including pantoprazole in Schedule 3 (for the relief of heartburn and other symptoms of GORD) the NDPSC had previously accepted that both the drug and the indication were suitable for self-treatment with pharmacist advice.

· A Schedule 3 product was launched in late 2008. At that time a package of educational materials was developed and made available to pharmacists. The educational material has been reviewed previously and was of a generally high standard. Data from an Australian audit of interactions between customers and

pharmacists suggested that pharmacists were willing and able to provide considered advice to potential purchasers of pantoprazole, including appropriate referral of some consumers to medical care.

- Usage data since the launch of the product suggested that there was relative under-usage in comparison with less efficacious products available in supermarkets, where there was no access to professional advice, and therefore no potential for appropriate referral when it would be desirable.
- The present application has provided a well supported argument in favour of the applicant's contention that there were potential public health benefits to be gained by allowing direct-to-consumer advertising of Schedule 3 pantoprazole products. These included the earlier identification of consumers who required medical attention for their GORD, and the more effective treatment of symptoms of patients who were suitable for self-medication and who have failed to derive sufficient benefit from antacids and H2 receptor antagonists (H2RAs).

Further points from the evaluator's report

The evaluator noted that much of the material in this evaluation report was repeated from the February 2010 evaluation report as many of the facts and arguments were unchanged. Substantial additions have been summarised below.

Much of these additions consist of further data, including safety up-date data and clinical trial data, relating to the safety and wide therapeutic index of pantoprazole. The evaluator found that these data were convincing. These were all relevant to the previous Schedule 3 rescheduling decision which has already been implemented, but did not progress the matter of inclusion in Appendix H.

The applicant contended that the ability to advertise to consumers would:

- address any consumer misconception that heartburn does not need medical intervention;
- provide a means of raising awareness of the pharmacist's ability to provide advice and more effective treatment for heartburn;
- drive more heartburn sufferers into the pharmacy, therefore positively impacting on public health by promoting a better use of professional expertise; and
- in conjunction with the pharmacist educational materials, facilitate early identification of atypical symptoms or 'red flag' symptoms that require medical referral, leading in turn to more timely medical consultation with resultant cost savings, including improved work productivity.

The evaluator noted that while many of these points were not directly supported by evidence in the application, they seemed likely to be true on the basis of experience to date with pantoprazole and with other advertised OTC products.

The applicant also argued that allowing advertising of the product would meet the primary purposes for which such advertising was intended; namely:

- protection of public health by identifying customers whose condition warranted referral to their GP, and who may otherwise have not sought such advice and thus remained unidentified; and
- improvement in health outcomes by checking that consumers with heartburn were being offered the most appropriate, evidence-based treatment for their condition.

The evaluator accepted these arguments, although noted that it was likely that there would still be a considerable number of people with heartburn who continue to self-medicate with readily available remedies, and who therefore would not attend the pharmacy. It was reasonable to presume that consumers with symptoms at the severe end of the spectrum were more likely to attend for professional advice, and this would be an appropriate use of professional resources for the community.

Applicant's Response to the Evaluation Report

The applicant agreed with the conclusions and recommendations made in the evaluation report. The applicant asserted that it was apparent that, based on the data supplied, the evaluator agreed that the applicant provided a well supported argument demonstrating that public health benefits were to be gained by allowing direct to consumer advertising of pantoprazole.

In light of the positive recommendations, the applicant wished to respond only to two areas of the report – to the comment that many of the points supporting a public health benefit were not directly supported by evidence; and secondly to the potential for increased workload as a result of more consumers seeking pharmacist advice.

Evidence to support public health benefits

- Asserted that data in the application supported that many frequent heartburn sufferers were taking products purchased in general sales outlets and not seeking healthcare professional advice. These data supported the contention that many consumers did not think that heartburn warranted talking to a healthcare professional.
- Direct evidence was also provided from an Australian Pharmacy Audit which supported that when consumers did present to the pharmacy they were provided with appropriate advice and referred for medical attention where needed.
- Noted that the ability to advertise to consumers enabled communication via a vast array of media. The application provided examples of the European advertising materials for this substance, including a link to a branded consumer website. The website contained simple to use information directly addressing consumer misconceptions about heartburn. It also directed the consumer to speak to their pharmacist about their condition. Argued that this demonstrated that advertising

could be used to inform and educate consumers regarding the need for medical intervention and direct them to seek health care professional advice.

- Notwithstanding the above, agreed that the application lacked direct data specifically demonstrating how advertising of pantoprazole would or could influence the consumer and prompt them to visit the pharmacy. The applicant asserted that its conclusions in this respect were based on observations from other therapeutic fields in the industry. For example, it was accepted that advertising plays a role in informing consumers about OTC medicines and driving them to seek pharmacist advice. Indeed, as an example, the advertising of nicotine replacement therapy was cited as a significant driver in the reduction of the prevalence of smoking in Australia.

Potential increase in workloads

- Argued that the overall aim of advertising was to prompt consumers to seek pharmacist advice. The applicant concurred with the evaluator that this was unlikely to be a concern. Asserted that otherwise it would have been raised as an issue by key pharmacy groups.
- Dramatic increases in sales of other Schedule 3 products were documented in the literature. For example, it was reported that when nicotine replacement therapy was rescheduled to Schedule 3 in 1997 sales increased by 1117 per cent in one year. Despite this dramatic increase, and the requirement for pharmacist intervention at the point of purchase, there was no indication that pharmacy was unable to cope with the additional workload.
- The evaluator agreed that, based on the data supplied, there was probable under usage of pantoprazole in comparison with less efficacious products available in supermarkets where there was no access to professional advice.
- In addition, the evaluator agreed that the arguments presented in the application were reasonable and that the data provided supported the above public health benefits. The evaluator identified no negative impact of advertising of this substance.

February 2011 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX.

None of the February 2011 pre-meeting submissions opposed listing pantoprazole in Appendix H. The submission from XXXXX, however, framed its support in terms of listing both pantoprazole and rabeprazole in Appendix H XXXXX. XXXXX also qualified its support by asserting that Appendix H status should be consistent across the spectrum of PPIs listed in Schedule 3.

Additional details from the pre-meeting submissions are provided below.

XXXXX

In addition to its application and response to the evaluator's report, XXXXX also submitted a pre-meeting comment. Main points included:

- Reiteration of a number of arguments from its application and response to the evaluator's report.
- In addition, used this as an opportunity to update relevant data in its application, noting that several months had passed since the application was lodged. Members noted that this new information was not seen by the evaluator. In particular:
  - Advised that pantoprazole was currently the only Schedule 3 PPI with directly relevant market use data in the Australian setting. Provided a reference to published data showing supply in the Australian setting.
  - Asserted that newly published data (January 2011) further confirmed that the potential for an interaction between PPIs and clopidogrel was not a class effect. The reference supported the presence of a true metabolic drug-drug interaction between clopidogrel and omeprazole and that the interaction was not a class effect.
  - Argued that this data support the making of scheduling decisions based on the safety of individual active ingredients, rather than PPIs as a class.
  - Argued that a recently published paper also further supported the argument that driving more people with heartburn into the pharmacy would positively impact public health. This research asserted that when determining the suitability of the pantoprazole product, pharmacists were appropriately identifying customers with red flag symptoms and referring them to their GP for further investigation.
  - Since lodging the application, no serious adverse events have been received by the applicant concerning pantoprazole XXXXX.

XXXXX

XXXXX.

Expressed continued support for the Appendix H listing of pantoprazole, noting its efficacy and safety profile equivalent to other over-the-counter heartburn pharmacotherapies.

Asserted that Appendix H listing would encourage more patients with heartburn to speak with the pharmacist about their condition. This was likely to have two positive health outcomes:

- Patients would receive the most appropriate OTC therapy for their condition.
- Patients with more severe or red flag symptoms would be referred to their GP earlier for clinical review.

Asserted that with more than 2 years market experience of Schedule 3 pantoprazole, it was time to allow the public to be informed about this treatment option.

XXXXX

XXXXX contended that consumers ought to be made aware of products such as Schedule 3 pantoprazole and supported the proposed inclusion in Appendix H. The submission's discussion in support of this position included:

- The arguments recorded in the February 2010 NDPSC Record of Reasons from the applicant and evaluation report supporting Appendix H listing (as detailed under "February 2010 NDPSC Consideration") were noted.
- The NCCTG Guidelines on Schedule 3 advertising was also noted. XXXXX asserted that these guidelines have been met in relation to pantoprazole and offered comments in relation to each of the guidelines, including the following:

  Potential public benefit

  - Recalled the February 2010 applicant's argument that advertising would provide public benefit, noting that the evaluator agreed with this assessment (as did some members of the NDPSC).
  - Contended that advertising would prompt consumers to seek advice from a pharmacist and that such advice may result in more effective treatment or earlier identification of consumers who require medical intervention.
  - Suggested that inclusion in Appendix H would also provide a public benefit through potential reduction in unnecessary visits to GPs.
  - Further, while pantoprazole remains in Schedule 3, the pharmacist would continue to act as a final safeguard between the consumer and the product. No matter what the effect of advertising, the consumer can not purchase the product except with the intervention of the pharmacist. Asserted that this ought to be kept in mind when weighing the benefits of inclusion in Appendix H against any potential risk that advertising may inappropriately influence demand.

  Likelihood of advertising leading to inappropriate patterns of use

  - Reiterated the applicant's position that there was no evidence that the advertising of Schedule 3 pantoprazole would result in inappropriate use.

  The wider regulatory system

  - Noted the current advertising requirements of the *Therapeutic Goods Act 1989*, the Therapeutic Goods Regulations 1990 and the Therapeutic Goods Advertising Code.

The responsibility of pharmacists to be involved

- Reiterated the applicant's arguments that educational tools and treatment protocols have been prepared in relation to pantoprazole in order to ensure that pharmacists are able to provide appropriate professional advice.

Availability of Consumer Medicine Information (CMI)

- Noted that the CMI was available in relation to Schedule 3 pantoprazole.

Desire for consumers to manage their own medication

- Argued that, in general, there was no doubting the interest that consumers have in accessing medical and pharmaceutical information and in taking control of their medication and treatment. In particular, the growth of the gastrointestinal category in supermarket products showed the willingness of consumers in this category to manage their own medication.

· Also reiterated a number of the applications' arguments against 52E.

· Argued that the advertising of Schedule 3 pantoprazole was justified by the combination of the safety profile, history of safe use, indication for short-term use, the ability of pharmacists to provide professional advice to ensure the quality use of medicines, the preparation of pharmacy through education and information provision and the potential public health benefit resulting from increased awareness of all available treatments.

XXXXX

XXXXX arguments in support of pantoprazole listing in Appendix H included:

· A sponsor of pantoprazole XXXXX was fulfilling the commitment it made prior to the rescheduling to Schedule 3 to work with pharmacy stakeholders in an ongoing manner. This included the delivery of education, training and resources to pharmacists nationally, and consultation regarding consumer based research.

· Noted that there was scope for more comprehensive education to be delivered to the non-pharmacist staff sector of the pharmacy workforce. Believed that Appendix H listing for pantoprazole would appropriately enable further investment in education events and resources for non-pharmacist pharmacy staff.

· Noted that advertising to the public occurs for several Schedule 2 and unscheduled products used to treat uncomplicated GORD. The inclusion of pantoprazole in Appendix H would therefore better align with the information available to consumers regarding this category of products. Asserted that this would assist consumers in making an informed choice.

XXXXX

XXXXX believed that a consistent approach should be applied to Appendix H listing for Schedule 3 rabeprazole and pantoprazole and that there were significant potential benefits

in terms of increased awareness of more efficacious treatment options. The arguments in support of this position included:

- Stated that rabeprazole and pantoprazole could be considered to be equivalent in efficacy, though there may be some minor differences in pharmacokinetic profile and potency. Asserted that both pantoprazole and rabeprazole should be viewed similarly in terms of Appendix H.
- Noted that pantoprazole had been marketed since November 2008. Rabeprazole was launched in January 2010.
- Asserted that the risks of misuse were low and the safety of PPIs as a group was equivalent to that of H2RAs, which were advertised.
- Stated that availability in itself did not equate to public or consumer awareness, and many reflux sufferers would be unaware that pharmacists could recommend a PPI for frequent heartburn associated with GORD. Some of these consumers were chronic users of antacids (with low efficacy) and H2RAs. Many of these consumers would benefit from a course of PPI treatment but were unaware of its availability. Increased consumer awareness of a more effective treatment such as a PPI would be beneficial to this group of consumers.
- Asserted that use of a short course of PPIs was cost effective and provided cost benefits and improvement to quality of life for GORD sufferers. Stated that untreated GORD was a significant cause of absenteeism and treatment of GORD with on-demand rabeprazole was found to improve patients' quality of life and psychological wellbeing.
- Contended that there was little risk to the community of advertising PPIs for symptomatic treatment of GORD. OTC PPIs were available as 14-day treatment packs and due to the short length of a course of treatment there was very little risk that serious symptoms would be masked or that diagnosis of serious conditions would be delayed. Pharmacists would continue to have control of the product at the point of sale and would refer any patients with "alarm" symptoms.
- Pharmacists have guidelines for supply of PPIs, and due to the length of time that pantoprazole has been marketed they are familiar with the indications and contraindications and when to refer. Thus the potential inappropriate use for non-GORD indications was low.
- Advised that, XXXXX, it sought the opinions of specialist gastroenterologists as to the appropriateness of direct-to-consumer advertising and the equivalence of PPIs in general. Referred to a letter from XXXXX who provided the opinion that there was little risk of harm from direct-to-consumer advertising of PPIs.
- Provided extensive arguments, data and references regarding the equivalence of rabeprazole and pantoprazole.
- Noted the February 2010 position of the NDPSC that a consistent approach for all PPIs should be undertaken in relation to Appendix H listing.

XXXXX

XXXXX did not object to the inclusion of pantoprazole in Appendix H noting, however, that such inclusion should be consistent across the spectrum of PPIs listed in Schedule 3 and must manage the risk for the potential advertising of related Schedule 4 products containing PPIs. Its arguments in support of this position included:

General position on advertising Schedule 3 products

- While acknowledging that responsible advertising of Schedule 3 products may have some public benefit by prompting health professional intervention through raising consumer awareness of relevant health conditions and the availability of possible treatments, raised concerns about consumers requesting specific Schedule 3 products based solely on an advertisement.
- Noted that clever product advertisement could significantly influence a consumer's decision on how a particular condition should be managed, making it difficult for pharmacists to effectively meet their professional responsibilities by assessing the appropriateness and safety of a direct product request for a Schedule 3 medicine.
- While supporting direct-to-consumer advertising that advises consumers with specific conditions to consult their pharmacist, it was generally reticent to support including listings in Appendix H, particularly newly approved Schedule 3 listings that have been down-scheduled from Schedule 4.

Need to advertise availability of PPIs

- Noted that some consumer and public benefit from direct-to-consumer advertising was possible. In the instance of pantoprazole and other Schedule 3 PPIs, this included:
  - Increased consumer awareness of an effective treatment. Consumers that suffer with more frequent bouts of heartburn or reflux would be more aware of an effective treatment and may be prompted to seek health professional input.
  - Increased awareness of new, effective treatments for heartburn and reflux may prompt consumers who regularly purchase antacids or H2RAs (such as ranitidine) from supermarkets, without any review, to consult their pharmacist for more information. This would provide their pharmacist with an opportunity to assess and provide more appropriate therapy options and/or lifestyle support, or to refer to a GP if required.

Risk of irresponsible advertising or adverse public outcomes from advertising

- Believed that there was no more concern with the advertising of Schedule 3 PPIs than with antacids and H2RAs. Considering the interaction profile of antacids, and the fact that H2RAs were only indicated for the short-term management of reflux symptoms without medical advice, the advertising of Schedule 3 PPIs would be in the public interest by raising awareness of other therapies and prompting consultation with a health professional.

- Asserted that the safety profile of PPIs was reasonable with no abuse potential risk to justify restricting direct-to-consumer advertising of Schedule 3 PPIs.
- Noted that PPIs were unusual in that the same medicine was also listed in Schedule 4. Should the listing of pantoprazole and other PPIs within Appendix H be supported, there should be caveats attached to ensure that there was no advertising, whether accidental or intentional, of related prescription only products. Suggested that this may be achieved by only permitting the advertising of Schedule 3 products in which the brand name is distinct from that of the Schedule 4 counterpart. Members noted that scheduling had no control over the approval process for individual advertisements apart from the Appendix H status of the substance.

Pharmacists' familiarity with protocols and responsibilities

- Stated that with the availability of Schedule 3 pantoprazole since May 2008 pharmacists have had ample time to become accustomed to protocols and responsibilities associated with the supply of Schedule 3 PPIs.
- Although the PSA protocol was specific for pantoprazole, it could easily be applied to other Schedule 3 PPIs as most of the individual processes and considerations were non-specific.
- There was concern about a potential interaction between PPIs and clopidogrel which may reduce the effectiveness of clopidogrel and increase a patient's risk to thrombo-embolic events. However, the European Medicines Agency recently indicated that the only PPIs concerned were omeprazole and esomeprazole and there were no solid grounds to extend warnings to other PPIs.
- Noted the previous NDPSC rejection of proposals to list various PPIs in Appendix H. Asserted that circumstances have now changed, with one of the main risks identified (the potential interaction with clopidogrel) no longer being of such concern. Contended that pharmacists were sufficiently capable of mitigating any remaining risk in the same manner that they do when dispensing PPIs and clopidogrel from a prescription.

XXXXX

Expressed continued support for pantoprazole to be listed in Appendix H. XXXXX. In particular, noted that the Australian Pharmacy Audit of the OTC management of heartburn:

- Indicated that half of customers who consulted with a pharmacist suffered from frequent heartburn for which a PPI (such as pantoprazole) was the most suitable therapy.
- Asserted that one in twenty pharmacist consultations resulted in a GP referral to investigate atypical symptoms. Hence a public health benefit (improvements in the quality use of heartburn medications) was demonstrated by encouraging consumers to speak with the pharmacist.

- Found no evidence that advertising would lead to inappropriate usage.
- Confirmed that pharmacists appropriately managed the use of pantoprazole in the Schedule 3 setting. In addition, when heartburn symptoms occurred less frequently or were mild, alternative therapies, such as antacids and H2RAs were recommended.

XXXXX

Noted that PPIs were well established as the gold-standard therapy for the management of GORD. Pantoprazole, like other PPIs, had an excellent safety profile, and its non-prescription availability posed no increased risk to patients who manage heartburn with over-the-counter medications.

Supported an Appendix H listing for pantoprazole. Asserted that one of the primary reasons for this was a pharmacy education programme implemented by a sponsor. Asserted that this programme guided pharmacists on the appropriate use of the product and had a clear mechanism for referring patients to a doctor for medical review, an initiative not promoted by other OTC treatment options.

Also noted the clinical audit (discussed above) which demonstrated that pharmacists play an important triage role in GORD management. Asserted that advertising of Schedule 3 pantoprazole would encourage more people to discuss their symptoms with a healthcare professional leading to an improvement in symptom management.

XXXXX

Supported the inclusion of pantoprazole in Appendix H. Also noted the clinical audit (discussed above) which indicated that pharmacists seemed to be implementing the use of OTC pantoprazole in an appropriate manner.

Argued that, compared with other OTC heartburn treatments, pantoprazole provided consumers with an incremental improvement in efficacy without a compromise in safety. Asserted that it seemed reasonable that as Appendix H listing was appropriate for other commonly used pharmaceutical agents, that pantoprazole be afforded the same regulatory status.

XXXXX

Supported including pantoprazole in Appendix H. Arguments in support of this position included:

- Noted that Australia has two and a half years of post-marketing experience with OTC pantoprazole. Stated that this Australian experience mirrors the post marketing experience from comparable overseas countries where OTC PPIs have been permitted to be advertised for a number of years (the UK, the USA, Sweden, Denmark and Norway).

- Asserted that a significant proportion of the population would benefit from OTC pantoprazole if they were made aware of its availability, resulting in improved health outcomes and a public health benefit.
- Stated that pharmacists were using the protocols developed by the sponsor and the PSA to ensure that only suitable patients would commence treatment and that, if necessary, patients would be referred to a general practitioner.

XXXXX

Arguments in support of including pantoprazole in Appendix H included:

- Noted the availability of OTC pantoprazole in Australia. Asserted that this allowed pharmacists sufficient time to establish pharmacy protocols for the OTC use of this medication.
- Asserted that advertising of Schedule 3 pantoprazole would inform heartburn sufferers about alternative treatments. Noted that as the product could only be purchased with the involvement of a pharmacist, the appropriateness of treatment would improve.

February 2010 NDPSC Consideration

In February 2010 the NDPSC rejected an Appendix H application for pantoprazole, primarily on the grounds that advertising of pantoprazole would potentially impair the ability of pharmacists to adequately carry out their professional responsibilities. Members noted the following points from the February 2010 NDPSC discussion:

- A Member expressed concerns with recent reports from the 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 and 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, including:
  - 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 both 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 usage 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 pharmacists 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 the applicant 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 pharmacists and peak organisations such as the PSA and PGA generally prefer not to have Schedule 3 products advertised directly to the public, in this instance it seemed that pharmacists and PGA 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 the applicant.

February 2010 Evaluation Report

The February 2010 evaluation report recommended that the application be approved, on the basis that Australian pharmacists had had a further year of experience (since the previous application) with the supply of pantoprazole under Schedule 3 conditions, that an audit of interactions between Australian consumers and pharmacists had indicated that pharmacists were willing and capable of giving appropriate advice, including whether or not to purchase the OTC product, and referral to medical care when required.

The evaluator asserted that these data provided sufficient evidence, in the view of the evaluator, in support of the contention that direct-to-consumer advertising in this case provided a net public health benefit to the Australian community.

February 2010 Pre-meeting Submissions

Pre-meeting submissions from a peak pharmacy body supported the proposal, as did submissions from gastroenterologists, including the co-author of the national reflux guidelines.

XXXXX opposed the inclusion of pantoprazole in Appendix H, arguing that 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.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members questioned the benefit of advertising of PPIs. A Member asserted that if pantoprazole was included in Appendix H, a consistent approach should be maintained for all PPIs to ensure awareness of multiple treatments. Another Member contended however that the aim of product advertising was to increase product awareness (and resultant market share), not to improve community awareness of a disease and all its available treatments. The Member noted that a television campaign aimed at increasing the awareness of GORD currently exists and an Appendix H listing for PPIs would not provide additional benefit to the public's awareness of available forms of treatment.

A Member asserted that GORD requires diagnosis by appropriately qualified practitioners (i.e. pharmacists). The Member also stated that unlike H2RAs, there was a risk that pantoprazole could mask symptoms of more serious disorders and advice was required before a treatment was selected. It was asserted that advertising of pantoprazole would transfer the responsibility of diagnosis onto the consumer which may inappropriately increase pressure on the pharmacist for supply of this product. Members also noted that PPI efficacy relies on consistent use over a longer period of time. A Member asserted that advertising may inadvertently reinforce inaccurate consumer expectations that PPIs, like some other GORD treatments, may be used as a "quick fix" and would not require adherence to treatment.

Members noted the factors outlined in the SPF for inclusion of substances in Appendix H. A Member noted that pantoprazole may appear to be a suitable candidate for Appendix H listing according to these factors. Other Members asserted however that the factors listed in the SPF are meant as a guide and Appendix H consideration is not limited to these.

Members generally agreed that pantoprazole should not be listed in Appendix H.

DELEGATE'S DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (d) presentation of the substance.

DELEGATE'S INTERIM DECISION

The delegate decided that the current scheduling of pantoprazole remained appropriate i.e. no Appendix H listing.

SUBMISSIONS ON INTERIM DECISION

XXXXX made a further submission requesting that the delegate vary the interim decision and include pantoprazole in Appendix H. The submission also made several points, summarised below:

- Asserted that the original application addressed each of the matters for consideration of a product for Appendix H listing, as specified in the NCCTG Guidelines for brand advertising of substances included in Schedule 3 of the SUSMP.
- Noted that the evaluation and all pre-meeting submissions supported Appendix H listing.
- Asserted that the issues raised by some ACMS Members were more relevant to the scheduling of pantoprazole and had minimal bearing on the application for Appendix H listing.
- Claimed that the delegate, by referring the proposal to the ACMS, has intimated that the current scheduling (i.e. no appendix H listing) may not be appropriate.

The submission also sought to address points raised by the ACMS in their discussion:

Benefit of advertising of PPIs

- Noted that the evaluator accepted the application's assertion that advertising would protect public health by identifying customers whose condition warranted referral to their GP, and who may otherwise have not sought such advice. Asserted also that advertising would result in improvement in health outcomes by checking that consumers with frequent, moderate to severe heartburn are being offered the most appropriate, evidence-based treatment for their condition. Stated that ACMS Members did not dispute this argument or the evaluator's conclusions.
- Disagreed with a Member's comment that a consistent approach for all PPIs should be adopted in relation to advertising. Stated that a class approach would not be appropriate at this time because pantoprazole was the only PPI in Australia with

significant in-market experience (over 2.5 years) and was the only PPI listed in Schedule 3 with published data demonstrating appropriate supply in the Australian setting. Reiterated that scheduling decisions and entries into the SUSMP were substance based, not class based, specifically noting published data of a metabolic non-class drug-drug interaction between clopidogrel and omeprazole. Asserted that scheduling decisions should consider the safety profiles of individual active ingredients, rather than PPIs as a class.

- Noted the existing television campaign referred to by an ACMS Member. Asserted that the campaign was aimed at directing consumers to their GP for assessment and (potentially) a prescription and therefore did not improve community awareness of Pharmacy based treatment options. Stated that according to a Gut Foundation report there was a high degree of reluctance amongst Australian consumers to consult with a GP for heartburn.
- Reiterated the potential benefits of advertising contained in the application.

Diagnosis issues

- Reiterated the evaluator's comment that the safety data for pantoprazole were convincing and the safety of self management with the advice of a pharmacist was recognised by the 2005 NDPSC rescheduling decision. Stated that none of the Members disputed the current scheduling status of pantoprazole.
- Asserted that Members' comments in relation to diagnosis and risk of masking symptoms were relevant to the scheduling of pantoprazole not the Appendix H application. Asserted that the risk of OTC pantoprazole masking an underlying condition requiring medical attention was similar to that of other approved heartburn OTC medications.
- In relation to a Member's comment regarding advertising transferring responsibility of diagnosis onto the consumer, stated that if additional pressure on pharmacists was an issue it would have been raised by key pharmacy groups. Asserted that support from the PSA would suggest that this was not an issue.
- Reiterated the application's point that a published Australian audit of pharmacy practice demonstrated that pharmacists were able to determine which customers had frequent heartburn, appropriately recommend treatment, and appropriately identify the presence of "red flag" symptoms and refer customers with severe symptoms to their GPs.
- Stated that although pantoprazole was a suitable choice for 77 per cent of patients, pharmacists only recommended pantoprazole to 69 per cent of patients and only 58 per cent purchased the product. Asserted that this demonstrated that pharmacists were exercising their own clinical judgement in determining the appropriateness of this product and consumers were heeding that advice (as demand for purchase did not outweigh recommendation rates). Asserted that consumers were exercising caution, listening to the pharmacist and not unrealistically demanding a product which may not be clinically justified in their case.

- Disagreed with a Member's comment that advertising may reinforce inaccurate expectations of PPI use and asserted that the pharmacist would be able to adequately explain pantoprazole use, further reinforced by the TGA approved CMI and package leaflet. Stated that the pharmacy audit did not highlight any cause for concern regarding consumer label comprehension for this substance. Asserted that examples of European advertising submitted with the application did not suggest that the portrayal of the product would conflict with the approved OTC Prescribing Information. Reasserted that the inclusion of pantoprazole in Appendix H would not result in the advertising for any indication other than those included in the Australian Register of Therapeutic Goods.

Factors not outlined in the SPF

- Asserted that the guidelines in relation the Appendix H considerations do not provide scope for the need to consider "other factors". Reasserted that the application addressed the Appendix H factors in the guidelines and raised concerns that as these "other factors" have not been disclosed it is not possible for them to be addressed.

Issues raised in pre-meeting public submissions

- Noted concerns regarding the inadvertent advertising of related prescription-only products and the suggestion of distinct brand names for Schedule 3 and 4 products. Asserted that this scenario was neither new nor unique to PPIs and had not previously been raised in relation to Appendix H listings. Gave examples of existing Appendix H listings for diclofenac and ranitidine and asserted that the naming of pantoprazole products was sufficiently distinct in comparison.

DELEGATE'S FINAL DISCUSSION

The delegate considered the only submission received in response to the interim decision and noted that it reiterated many points which were previously raised in the application and the pre-meeting submissions which were considered as part of the ACMS's and delegate's interim discussions.

In response to certain comments, the delegate clarified that neither a referral to an advisory committee nor the publishing of a delegate's proposal were indicative of a delegate's scheduling intention or a delegate's views on the appropriateness of the current scheduling.

The delegate also noted the submission's comment in relation to factors outlined in the NCCTG Guidelines for brand advertising of substances included in Schedule 3. The delegate noted section 32 of Part 3 of the SUSMP stating that Schedule 3 substances are not allowed to be advertised unless listed in Appendix H. The delegate clarified that inclusion of a Schedule 3 substance in Appendix H was by exception following consideration of the substance's specific risk-benefit profile. The delegate reiterated the ACMS comment that the factors listed in the SPF guidelines were meant as a guide and inclusion of a Schedule 3 substance in Appendix H should not be assumed based only on

these. The delegate asserted that the balance between potential public health benefit and the protection of public health and safety was fundamental to these considerations.

The delegate also reiterated concerns raised in a pre-meeting submission in relation to the effect of advertising on a consumer's decision-making in choosing medicines. The delegate agreed that the interim decision was appropriate and that pantoprazole should not be listed in Appendix H.

DELEGATE'S FINAL DECISION

The delegate confirmed that the current scheduling of pantoprazole remained appropriate i.e. no Appendix H listing.

2.2.3 RUPATADINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of rupatadine and decided to seek advice from the ACMS on the following:

Rupatadine – proposal to include in Appendix K.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that rupatadine be included in Appendix K. The Committee recommended an implementation date of 1 September 2011 (three months following delegate's final decision).

BACKGROUND

Rupatadine is an antihistamine with platelet-activating factor antagonist activity under investigation for symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria (CIU) in adults and adolescents (over 12 years of age).

In December 2010, a delegate considered an application to register rupatadine and decided that a Schedule 4 entry was appropriate. The delegate also noted data indicating sedation effects associated with rupatadine and decided to refer a proposed Appendix K entry for advice from the ACMS.

SCHEDULING STATUS

Rupatadine is listed in Schedule 4.

INITIAL SUBMISSIONS

A pharmacology evaluation was undertaken as part of the TGA registration consideration. The matter was also referred for advice to the Advisory Committee for Prescription Medicines (ACPM). XXXXX. In relation to the scheduling proposal under consideration, the TGA provided the following information:

- Noted that rupatadine appeared to have sedating properties at a dose of 10 mg, with a dose-response relationship at higher doses.
- Stated that the most common adverse event associated with rupatadine was somnolence (9.5 per cent), compared to the frequency of somnolence associated with fexofenadine (7.3 per cent) and loratadine (1.2 per cent).
- Noted that patients' reasons for discontinuation were incompletely recorded, however fatigue, somnolence and asthenia were noted.
- Noted that hydroxyzine 50 mg (included in Appendix K) had a greater effect than rupatadine 10 mg in impairing driving performance, however noted that this could not be regarded as strong evidence that rupatadine did not impair driving performance.
- Noted that postmarketing data had one report of disorientation; however fatigue or asthenia were not reported.
- Noted that the evaluator did not accept the claim that rupatadine was non-sedating. In response, the applicant provided a table showing the incidence of somnolence, disturbance in attention, sedation and fatigue of rupatadine compared to placebo and other anti-H1 compounds (cetrizine, ebastine, loratidine and desloratidine – Members noted that of these, only cetirizine is currently included in Appendix K). The registration applicant asserted that the data in this table demonstrated that there were no differences between rupatadine 10 mg and other second-generation antihistamines.

Pre-meeting Submissions

XXXXX did not support inclusion of rupatadine in Appendix K nor the specific scheduling of rupatadine in Schedule 4. Members noted that the inclusion of rupatadine in Schedule 4 was a final decision implemented from 1 January 2011 and was not referred for advice. The submission made a number of points in relation to the proposed Appendix K entry, summarised below:

- Asserted that statement 90: "*This preparation is to aid sleep. Drowsiness may continue the following day. If affected do not drive or operate machinery. Avoid alcohol.*" was not appropriate as rupatadine was not indicated as a sleep aid.
- Asserted that statement 40: "*This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery.*" was not appropriate. Asserted that study data demonstrated that rupatadine 10 mg combined with alcohol did not produce greater cognitive and psychomotor

impairment compared with alcohol alone and little if any additive effect to alcohol induced impairment.

- Asserted that statement 39: "*This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol.*" was not appropriate. Asserted that published clinical study data with rupatadine 10 mg do not support a warning corresponding with not driving a vehicle or not operating machinery nor does clinical data support the statement to avoid alcohol.
- Asserted that second generation antihistamines were *relatively* non-sedating compared with first generation antihistamines. Suggested that a non-sedating second generation antihistamine with zero somnolence did not currently exist and it should be sufficient to include notification of potential for sedation in the Product Information documents.
- Stated that consistent with other non-sedating second generation antihistamines available in Australia for which somnolence is reported in less than 10 per cent of patients (excluding cetirizine) somnolence occurred in 9.5 per cent of rupatadine recipients.
- Asserted that there was a lack of CNS effects such as cognitive and psychomotor impairment shown in both clinical and preclinical studies for the recommended therapeutic dose of rupatadine 10 mg.
- Stated that rupatadine 10 mg combined with alcohol did not produce greater cognitive and psychomotor impairment compared with alcohol alone however alcohol with higher than the recommended rupatadine dose (20 mg) and therapeutic doses of cetirizine (10 mg) and hydroxyzine (25 mg) did produce greater cognitive and psychomotor decline than for alcohol alone.

The submission also provided a table of findings from human studies on somnolence related to varying dosages of rupatadine, hydroxyzine and cetririzine.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members noted that as a class, all non-sedating histamines are associated with idiosyncratic sedation effects. Members specifically noted that in the UK all non-sedating antihistamines have reports of sedation and contain wording on labels warning against potential drowsiness. A Member asserted that label warnings for these drugs need to be assessed on a case-by-case basis.

Members discussed the sedation potential of rupatadine. A Member noted that although rupatadine was classified as a non-sedating histamine, there was ambiguity regarding its sedation effects. The Member asserted that somnolence was a common side effect associated with rupatadine and patients should be aware of this potential. Another Member asserted that sedation potential can be explained by a pharmacist at the time of dispensation. However other Members agreed that a label would ensure access to information in addition to advice received from the pharmacist.

Members agreed that there was insufficient evidence that sedation was not an issue in rupatadine use. Members agreed that there was a need for rupatadine products to be labelled with a sedation warning.

Implementation date

Members noted that the delegate's final decision associated with this matter was expected to be published in June 2011. Members generally agreed that there was no need for a delayed implementation date and recommended an implementation date of 1 September 2011 (three months following the delegate's final decision).

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of use; and (d) labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include rupatadine in Appendix K. The delegate decided on an implementation date of 1 September 2011 (three months following publication of the delegate's final decision in June 2011).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that rupatadine be included in Appendix K. The delegate also confirmed an implementation date of 1 September 2011.

Appendix K – New entry

RUPATADINE

2.2.4 TAFLUPROST

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of tafluprost and decided to seek advice from the ACMS on the following:

Tafluprost – proposal to include in Appendices D and L.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the scheduling of tafluprost remain unchanged (i.e. no new Appendix D or L entry).

BACKGROUND

Tafluprost is a synthetic analogue of dinoprost (a prostaglandin F2α) indicated for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

In December 2010, a delegate considered an application to register tafluprost eye drops for the above indication and decided that a Schedule 4 entry was appropriate. The delegate also noted reproductive toxicity data which raised concerns with regard to use of tafluprost in pregnancy. The delegate decided to refer proposed Appendix D and Appendix L entries for advice from the ACMS.

SCHEDULING STATUS

Tafluprost is listed in Schedule 4.

INITIAL SUBMISSIONS

A pharmacology evaluation was undertaken as part of the TGA registration consideration. The matter was also referred for advice to the Advisory Committee for Prescription Medicines (ACPM). XXXXX. In relation to the scheduling proposal under consideration, the TGA provided the following information:

- Effects on the contractile activity of the isolated XXXXX uterus were seen with tafluprost.
- There was placental transfer of tafluprost and its metabolites XXXXX; also there was excretion in milk, after topical administration.
- Tafluprost (IV) was teratogenic XXXXX. XXXXX was considerably more sensitive to tafluprost compared to XXXXX.
- XXXXX there were still-births and death XXXXX suggesting that tafluprost may have a low risk of being an abortifacient.
- The evaluator recommended a Pregnancy Category D classification:
  Category D: Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.
- *In vivo* and *in vitro* studies showed no evidence of genotoxicity and no carcinogenicity was seen XXXXX.

- The evaluator noted that the safety profile of tafluprost was slightly worse than its comparators, latanoprost and timolol. However this statement was not agreed to by the sponsor, who provided further data to the TGA on adverse events comparing differences between groups.

Appendix D

Members noted that Appendix D lists substances for which additional controls on possession and supply are required. Normally, substances listed as Pregnancy Category X are included in Appendix D. Substances listed in Appendix D, paragraph 1 are available only from, or on the prescription or order of, an authorised medical practitioner. Dinoprost, a substance related to tafluprost used in the termination of pregnancy, is listed in Schedule 4 and Appendix D, paragraph 1. However other prostoglandins used in the treatment of glaucoma and ocular hypertension (latanoprost, travoprost and bimatoprost) are only listed in Schedule 4.

Appendix L

Members noted that labelling requirements for prescription medicines are regulated by the TGA. However, medicines prepared by compound pharmacies are not subject to TGA labelling regulations. Appendix L, Part 2 lists additional labelling requirements for human medicines. Medicines containing substances included in Appendix L must not be dispensed unless labelled with the warning statement(s) specified in column 2 of the table.

The Committee noted that levocabastine (an antihistamine used in eye drops for the treatment of allergic conjunctivitis) was listed in Appendix L with the warning statement 62 "*Do not use if pregnant*". Levocabastine was listed as a Pregnancy Category B3 drug: *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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

EXPERT ADVISORY COMMITTEE DISCUSSION

Members discussed the proposed Appendix D entry for tafluprost. The Committee noted the teratogenic effects of tafluprost and that optometrists may be seeking to prescribe these products. A Member asserted that due to the product's presentation, patients may inadvertently assume that tafluprost is benign and an Appendix D entry may be necessary to reinforce the concerns associated with the substance. However, other Members disagreed and asserted that restrictions associated with a Schedule 4 entry (which ensure management by a medical practitioner) were sufficient to convey this message. Members agreed that given the seriousness of the indication additional restrictions on possession and supply were not warranted and an Appendix D entry was not recommended.

Members discussed the proposed Appendix L entry for tafluprost. A Member asserted that the public do not associate eye drops with a systemic effect on the body and an Appendix L entry could ensure patients use the product with caution. However, another Member stated that tafluprost is indicated for use in glaucoma and asserted that the risks from this use of tafluprost in pregnancy were low due to the average age of onset of glaucoma. A Member also asserted that patients should receive appropriate advice from the pharmacists regarding the risks associated with tafluprost when it is dispensed. Members generally agreed that an Appendix L entry for tafluprost was not warranted.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of use; (c) toxicity; and (d) labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided that the current scheduling of tafluprost remained appropriate (i.e. no new Appendix D or L entry).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that the current scheduling of tafluprost remained appropriate (i.e. no new Appendix D or L entry).

2.2.5 TAPENTADOL

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of tapentadol and decided to seek advice from the ACMS on the following:

Tapentadol – proposal to include in Appendices D and K.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that tapentadol be included in Appendix K with an implementation date of 1 September 2011 (three months following delegate's final

decision). The Committee also recommended that an Appendix D entry was not appropriate for tapentadol.

BACKGROUND

Tapentadol is a centrally acting analgesic that exerts its pharmacological effects primarily by binding to μ-opioid receptors. Its binding affinity is approximately 18 times less than that of morphine.

The US Drug Enforcement Agency lists tapentadol in Schedule II (the same category as morphine, oxycodone and fentanyl). The Committee on Narcotics Drugs in Germany listed tapentadol in SIII (the same schedule as hydromorphone and morphine).

Tramadol, a drug in the same class as tapentadol is currently listed in Schedule 4 and Appendix K. A pharmacology study concluded that tapentadol demonstrated abuse potential comparable to that of hydromorphone (listed in Appendix 8 and Appendix K).

In December 2010, a delegate considered an application to register tapentadol for the relief of moderate to severe pain and chronic pain unresponsive to non-narcotic analgesia and decided that a Schedule 8 entry was appropriate. The delegate also noted data on sedation effects, reproductive toxicity and abuse potential. The delegate decided to refer proposed Appendix D and Appendix K entries for advice from the ACMS.

SCHEDULING STATUS

Tapentadol is listed in Schedule 8.

INITIAL SUBMISSIONS

A pharmacology evaluation was undertaken as part of the TGA registration consideration. The matter was also referred for advice to the Advisory Committee for Prescription Medicines (ACPM). In relation to the scheduling proposal under consideration, the TGA provided the following information:

- The abuse potential of tapentadol has not been fully elucidated due to limited clinical experience. Tapentadol is known to provide analgesia at similar levels of narcotics analgesics such as hydrocodone, oxycodone and meperidine with a more tolerable side effect profile.
- Tapentadol adverse reactions include somnolence and lethargy. Dizziness and somnolence occurred in patients given tapentadol with similar frequency to those given oxycodone (listed in Schedule 8 and Appendix K).
- Tapentadol is a Category C pregnancy drug:

  Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

- Pre-clinical studies revealed teratogenic effects in animals. Specifically, effects on female fertility, embryofetal development / teratogenicity and postnatal survival were observed, mostly associated with maternotoxicity. No controlled teratogenicity studies in humans have been reported.
- Placental transfer of tapentadol was confirmed in rats. Low levels of tapentadol and tapentadol-glucuronide were detected in milk from lactating rats following oral dosing.
- In the delegate's view there were no pharmacology issues of concern. The safety issues identified could be adequately managed by the Schedule 8 classification, by appropriate statements in the product literature and labelling and by modifications to the risk management plan.

The October 2010 ACPM meeting recommended approval of tapentadol for the proposed indications. The minutes of the meeting reiterated many of the above points and did not provide any additional information on the proposal under consideration.

Pre-meeting Submissions

XXXXX stated that inclusion of tapentadol in Schedule 8 and Appendix K would result in appropriate and sufficient control to ensure the safe and appropriate use of tapentadol in Australia. The submission contended that an Appendix D listing for tapentadol was not warranted and would be inappropriate.

The submission also provided the following additional information:

- Noted that tapentadol shared pharmacological activities with pure μ-opioid analgesics (such as oxycodone and morphine) and with drugs with noradrenaline reuptake inhibitor activity (such as reboxetine and duloxetine). A Schedule 8 entry for tapentadol was consistent with the classification of other μ-agonists approved in Australia (oxycodone, morphine, etc) and other opioid analgesics.
- Asserted that overseas scheduling restrictions (i.e. US and Germany) were equivalent to a Schedule 8 listing and no additional controls had been recommended by overseas regulatory authorities.
- Supported inclusion in Appendix K, noting that tapentadol was associated with sedation effects (somnolence and lethargy). Stated that an Appendix K listing would be consistent with other μ-agonists associated with sedation effects approved in Australia and overseas (ie. oxycodone, morphine, hydromorphone, fentanyl and other opioids).
- Stated that an Appendix D listing would unnecessarily restrict the availability of tapentadol by limiting tapentadol prescription to particular specialities. Provided detailed information on tapentadol prescribing by different specialities.
- Asserted that a Pregnancy C classification and the existing teratogenicity data was not sufficient evidence for an Appendix D listing. Asserted that study results supported

the conclusion that tapentadol was not teratogenic in animals. Provided a summary of preclinical data on the teratogenic effects of tapentadol.

- Stated that experience of the effects of tapentadol administration during human pregnancy was limited to pregnancies incidentally occurring during the clinical trial program or post-marketing. Noted that 12 reports of pregnancies or positive pregnancy test have been received from females who received at least one dose of tapentadol. Stated that none of these reports included any evidence of teratogenic effects of tapentadol.
- Noted that the advice on the use of tapentadol in pregnancy provided in the TGA-approved Australian PI, together with its Category C classification, was appropriate and adequate to assist clinicians to make appropriate prescribing decisions and to prevent a broad, uncontrolled use of tapentadol in pregnant women.
- Stated that this advice was the same as that approved by the US and EU Regulatory Authorities for tapentadol. It was also the same advice as that approved for drugs with a similar mode of action, none of which were included in Appendix D.
- Stated that data from clinical trials and overseas post-marketing experience supported the view that tapentadol was being prescribed appropriately and that additional controls (beyond Schedule 8) would be unnecessary.

XXXXX did not support the listing of tapentadol in Appendix D, stating that it would restrict the prescription of tapentadol to pain specialists only. The submission also made the following points:

- Asserted that an Appendix D entry would have adverse effects for patients in their ability to access this medication in a timely and appropriate fashion due to waiting lists and additional administrative burdens on General Practitioners.
- Stated that General Practitioners should be able to prescribe tapentadol similarly to their ability to prescribe tramadol.
- Asserted that inadequate treatment of pain was the greatest risk for production of chronic pain. Stated that an Appendix D entry would increase the burden of chronic pain on the community due to increases in economic costs.

A submission from XXXXX (a rheumatologist) did not support listing of tapentadol in Appendix D or K. Members noted that the submission only addressed restrictions associated with Appendix D and assumed that Appendix K imposed similar restrictions. The submission made the following points in relation to the matter under consideration:

- Asserted that there was a large burden of chronic pain in the Australian community, much of which resulted from chronic musculo-skeletal disease. Stated that tapentadol would prove beneficial in the management of these patients, most of whom were seen in primary care by general practitioners or on referral to rheumatologists and other clinicians.

- Asserted that an Appendix D listing would increase long waiting times to gain access to specialist clinics.
- Asserted that a Schedule 8 and Pregnancy Category C listing would be sufficient to ensure that primary care and specialist clinicians safely prescribed tapentadol. Stated that the prescription of other Pregnancy Category C medications was appropriately managed through patient selection.

XXXXX did not support the inclusion of tapentadol in Appendix D. The submission made a number of points, summarised below:

- Stated that access to tapentadol through the primary care sector was important for appropriate pain management.
- Asserted that an Appendix D listing for tapentadol would increase long waiting times to gain access to specialist clinics, reducing the potential benefit of pain management centres.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members discussed the referred tapentadol Appendix K entry. Members noted that available data supported the inclusion of tapentadol in Appendix K and that pre-meeting submissions also supported the labelling of tapentadol with a sedation warning. Members agreed that an Appendix K entry was appropriate for tapentadol.

The Committee also discussed the inclusion of tapentadol in Appendix D. Members noted that while some of the pre-clinical data on tapentadol suggested support for an Appendix D entry, further data were contradictory. A Member noted the similarities between tapentadol and tramadol (not listed in Appendix D) and asserted that similar restrictions on access should be maintained. Other Members also asserted that additional controls on tapentadol would inappropriately reduce access to the medication and impose excessive waiting times for patients. Members agreed that an Appendix D entry for tapentadol was not appropriate.

Implementation date

Members noted that the delegate's final decision associated with this matter was expected to be published in June 2011. Members generally agreed that there was no need for a delayed implementation date and recommended an implementation date of 1 September 2011 (three months following the delegate's final decision).

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of use; (e) potential for abuse; and (f) labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include tapentadol in Appendix K. The delegate decided on an implementation date of 1 September 2011 (three months following publication of a delegate's final decision in June 2011).

The delegate also decided that an Appendix D entry was not appropriate for tapentadol.

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that tapentadol be included in Appendix K. The delegate also confirmed that an Appendix D entry was not appropriate for tapentadol. The delegate confirmed an implementation date of 1 September 2011.

Appendix K – New entry

TAPENTADOL

2.2.6 TOLVAPTAN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of tolvaptan and decided to seek advice from the ACMS on the following:

Tolvaptan – proposal to include in Appendices D and L.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the scheduling of tolvaptan remain unchanged (i.e. no new Appendix D or L entry).

BACKGROUND

Tolvaptan is a selective, competitive arginine vasopressin receptor 2 antagonist used to treat hyponatremia (low blood sodium levels) associated with congestive heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone (SIADH).

In March 2011, as part of a registration consideration of tolvaptan for the above indication, a delegate decided to create a new Schedule 4 entry for tolvaptan. The delegate also noted animal data with regard to use of tolvaptan in pregnancy and decided to refer proposed Appendix D and Appendix L entries for advice from the ACMS.

SCHEDULING STATUS

Tolvaptan is listed in Schedule 4.

INITIAL SUBMISSIONS

Tolvaptan is classified as a Pregnancy Category C drug:

> *Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.*

The registration application's summary of clinical safety included the following information in relation to the scheduling proposal under consideration:

- No pregnancy experience in tolvaptan subjects had been reported in clinical trials to date.
- A study of embryo-fetal development XXXXX showed increased post-implantation death and fetal malformations and a study of pre- and post-natal development XXXXX showed increased perinatal death and body weight suppression in the offspring, with oral administration of tolvaptan at 1000 mg/kg/day.
- Ongoing clinical trials mandate contraceptive measures for women of childbearing potential and exclude pregnant or lactating women.
- If pregnancy was confirmed for any person receiving tolvaptan, that person should be discontinued from tolvaptan therapy and monitored.

Discussion and conclusions from the registration application's toxicology summary stated:

- A battery of reproductive and developmental toxicity studies were conducted XXXXX which suggested that use of tolvaptan may cause foetal harm.
- Tolvaptan impaired fertility XXXXX (above 1000 mg/kg/day), was teratogenic XXXXX (above 100 mg/kg/day and 300 mg/kg/day, respectively), and adversely affected reproductive performance XXXXX (above 100 mg/kg/day).
- As evident developmental toxicities, including teratogenicity, were noted at a relatively lower exposure XXXXX, it was suggested that special caution should be addressed to women of childbearing potential.
- Although tolvaptan was excreted into the milk of lactating XXXXX it was not known whether tolvaptan was excreted into human milk.

· Tolvaptan was considered to pose no genotoxic or carcinogenic risk to humans.

Appendix D

Members noted that Appendix D lists substances for which additional controls on possession and supply are required. Normally, substances listed as Pregnancy Category X are included in Appendix D. Substances listed in Appendix D, paragraph 1 are available only from, or on the prescription or order of, an authorised medical practitioner.

Appendix L

The Committee noted that labelling requirements for prescription medicines are regulated by the TGA. However, medicines prepared by compound pharmacies are not subject to TGA labelling regulations. Appendix L, Part 2 lists some labelling requirements for dispensed human medicines. Medicines containing substances included in Appendix L must not be dispensed unless labelled with the warning statement(s) specified in column 2 of the table.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members discussed the proposed Appendix D tolvaptan entry. The Committee noted that Appendix D was a regulatory mechanism which was reserved for substances which pose a significant potential of adverse effects to the community. A Member asserted that due to the seriousness of the indication, it was likely that tolvaptan treatment would occur under the supervision of a medical specialist. The Committee agreed that an Appendix D entry was not warranted. A Member also noted that with increased market experience, the product may progress to being prescribed by non-specialist general practitioners. A Member asserted that an Appendix D entry would not allow this process to occur if such a need arose.

Members discussed whether an Appendix L entry was warranted. Members noted that tolvaptan would be used predominantly in hospital practice and generally agreed that an Appendix L entry would not be required.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of use; (c) toxicity; and (d) labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided that the scheduling of tolvaptan remained appropriate (i.e. no new Appendix D or L entry).

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that the current scheduling of tolvaptan remained appropriate (i.e. no new Appendix D or L entry).

3. MATTERS INITIALLY REFERRED TO ACCS-ACMS#2 – FEBRUARY 2011

3.1 METHYLSULFONYLMETHANE / DIMETHYL SULFONE

DELEGATE'S PROPOSAL

The delegate considered the scheduling of methylsulfonylmethane (also called dimethyl sulfone) and decided to seek advice from the joint ACCS-ACMS on the following:

Methylsulfonylmethane – consideration of inclusion of methylsulfonylmethane in Schedule 4 for human therapeutic use in concentrations greater than 1500 mg per dose unit. This consideration may also include methylsulfonylmethane for non-human use, mirroring the scheduling of dimethyl sulfoxide.

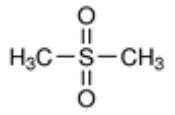
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the Schedule 4 and Schedule 6 entries for dimethyl sulfoxide be amended to specifically exclude dimethyl sulfone. The Committee additionally recommended an addition of a cross reference to the SUSMP index from methylsulfonylmethane to dimethyl sulfone. The Committee also recommended an implementation date of no more than 6 months after the delegate's final decision.

The Committee additionally recommended that the delegate refer the issue of labelling of supplements containing dimethyl sulfone with pregnancy and breastfeeding warnings to the TGA for consideration.

BACKGROUND

Methylsulfonylmethane (MSM) is an organic sulfur-containing compound that occurs naturally in a variety of fruits, vegetables, grains and animals and serves as a source of bioavailable sulfur. The IUPAC name and Therapeutic Goods Administration's (TGA) Australian Approved Name (AAN) of MSM is dimethyl sulfone and the structure is:



MSM is used as a supplement to improve the condition of hair, skin and nails, as MSM contributes sulfur to cysteine, a sulfur amino acid required for keratin production.

The TGA's Australian Register of Therapeutic Goods (ARTG) currently lists 29 products for human therapeutic use containing between 50 mg and 1500 mg MSM (indications include assistance in blood circulation, relief of rheumatism, rhinitis, symptoms of allergies, the management of osteoarthritic pain and maintenance or improvement of general well-being). All of these products were available as Listed (not scheduled) medicines.

MSM was also currently present in a number of products registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA). In many of these products MSM was not considered an active ingredient, it was instead considered to be a sulfur supplement. Two products were located on the APVMA's Public Chemicals Registration Information System which list 'dimethyl sulfone' as an active ingredient.

XXXXX submitted information on MSM to a delegate seeking a consideration of scheduling. A delegate agreed that this was a matter for a scheduling consideration and that advice from the joint ACMS-ACCS was needed.

SCHEDULING STATUS

MSM was not specifically scheduled in Australia or New Zealand. Dimethyl sulfoxide (DMSO) was included in Schedule 4, Schedule 6, Appendix E and Appendix F. The structural similarity of MSM and DMSO, together with the ease with which DMSO can be oxidized to form MSM, may indicate that MSM could be captured as a DMSO derivative under the scheduling of DMSO.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX submission noted that MSM can be prepared by oxidation of DMSO with hydrogen peroxide. XXXXX asserted that this suggested that MSM could therefore be classified as a derivative of DMSO and captured by the schedule entries for DMSO.

XXXXX noted that MSM was widely marketed via the internet, as well as being present in a number of listed products on the ARTG – listed products are unscheduled. XXXXX concluded that as there were several products containing MSM in the market, which appeared to have been assessed as complementary therapies, there was a need to clarify the scheduling of this substance.

February 2011 Pre-meeting Submissions

XXXXX

XXXXX did not support the proposal to schedule MSM, asserting that there was no valid safety concern to justify restricting the availability of MSM. The submission argued that:

- MSM's normal usage ranged from 1.5 to 10 g (daily divided doses).
- Few side effects were shown in a human study utilising 2600 mg/day.
- Toxicity studies conducted on rat showed no toxic effects up to 8 g/kg bw/d.
- Rat developmental studies established a NOAEL of 1000 mg/kg/day.
- Mutagenicity studies have shown negative results.
- Was unaware of any safety signal in Australia concerning MSM.

The submission further argued that the TGA had previously evaluated MSM as suitable for use in Listed medicines i.e. TGA judged it to be safe for use without supervision. The Listing notice did not have dose restrictions or label warning requirements.

The submission additionally asserted that although DMSO and MSM are chemically related they are not the same entity. Because of its greater safety MSM is preferred over DMSO.

The submission also requested that the AAN for MSM, dimethyl sulfone, be used.

XXXXX

XXXXX acknowledged it may be that MSM could be classified as a derivative of DMSO and therefore captured by the schedule entries for DMSO. However, it strongly opposed a Schedule 4 entry for MSM because it had been classed by TGA as a Listable active ingredient with no daily dose limit.

The submission also advised that the Interim Joint Expert Advisory Committee on Complementary Medicines (IJEACCM**)** evaluated DMSO in 2006 and concluded that 'limited pre-clinical and clinical data suggests that oral and topical toxicity of DMSO is relatively low in humans, even after repeated administration'. The submission argued therefore that there was no safety basis for restricting MSM based on daily dosage and questioned the justification for including a restriction on MSM. Members noted advice that the IJEACCM was a Committee established under the then proposed Trans-Tasman harmonisation process.

The submission also advised that the United States Pharmacopeia (USP) had an impurity limit of "*not more than 0.1 per cent of dimethyl sulfoxide is found, not more than 0.5 per cent of any other individual impurity is found; and the sum of all impurities, including dimethyl sulfoxide, is not more than 0.2 per cent*".

The submission proposed not including MSM as a new Schedule 4 entry and instead suggested amending the DMSO Schedule 4 entry to exclude MSM when compliant with the MSM monograph in the USP. Members noted that the USP did not set access restriction cut-offs, it sets a purity standard, which did not appear suited to being the basis of a schedule entry.

The submission also suggested that the AAN for MSM, dimethyl sulfone, be used.

XXXXX

XXXXX recommended that MSM products for use in animals should not be in Schedule 4.

The submission advised that sulfur is part of the nutritional requirements of animals and listed in the US National Research Council (NRC) as a requirement for dogs and horses. The APVMA specified that to be considered a nutritional supplement, any vitamin,

mineral or amino acid listed on the label must provide 25 per cent or more of the daily requirement for the particular animal species and age/class of animal. The NRC requirement for maintenance of an adult horse was 12 g of sulfur/day. MSM contains 34.06 per cent of sulfur therefore 9 to 36 g of MSM/day was required to provide 3 to 12 g (25 to 100 per cent of the nutritional requirement) of sulfur for a horse.

The submission argued that under the current proposal any nutritional supplement product providing greater than 1.5 g/day of MSM would be listed in Schedule 4. This would significantly increase the product's cost. The submission argued that minor problems, treated by MSM supplement, did not require a veterinarian to prescribe.

XXXXX.

Scheduling history of DMSO

The scheduling of DMSO was considered in August 1983 where it was noted that DMSO accelerated the speed of absorption of other medication through the skin. It was also noted that ocular toxicity characterised by lenticular opacity was the most significant toxic effect noted in the long-term testing leading to termination of all the clinical trials. Retrospective studies of over 20,000 cases of DMSO treatment in humans, with doses up to 60 g/day (average 30 g) and for periods up to 23 months, failed to reveal any proven cases of DMSO related ocular toxicity. The NDPSC therefore listed DMSO for therapeutic use in Schedule 4. Other uses of DMSO, including veterinary use when combined with no other therapeutic substances and for veterinary use in preparations containing copper salicylate as the only other therapeutic active ingredient, were listed in Schedule 6.

In November 1991 it was noted that clay poultice would have to be applied by hand which would cause the skin of the operator to be exposed to DMSO. The NDPSC also noted that even if the operator wore rubber gloves, little or no protection from exposure to DMSO could be assured. The NDPSC therefore recommended amending the Schedule 6 entry to include liquid preparations containing copper salicylate.

MSM Toxicology

A brief literature search failed to provide significant information on MSM toxicity. The only information located indicated that oral administration of MSM to pregnant rats at doses of 50, 500, or 1000 mg/kg/day over gestation days 6 to 20 (the period of organogenesis and histogenesis) did not result in any biologically significant alterations in the fetal or maternal body weights, nor in any structural malformations or fetal anomalies as evaluated by gross external, cephalic, visceral and skeletal examinations. Results indicated that the NOAEL for maternal and developmental toxicity of oral MSM was at least 1000 mg/kg/day. The authors concluded that these data support the mounting evidence of safety in-use of MSM.

COMMITTEE DISCUSSION

The Committee generally agreed that the relevant matters under section 52E (1) of the Act included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

Members considered whether current information supported a need to schedule MSM. Members noted that the scheduling of MSM had been originally referred for clarification, noting its wide availability as unscheduled despite potentially being captured by the DMSO scheduling. The referral had not argued whether or not such capture was appropriate.

A Member also reiterated the point from a submission that the TGA's classification of MSM (as dimethyl sulfone) as a Listed ingredient indicated that TGA had judged MSM to be safe for use without supervision. Other data from the submissions, while not extensive, were also generally supportive of the conclusion that MSM had low toxicity. A Member additionally noted that MSM occurs naturally, so there has been extensive human exposure, albeit at levels significantly lower than those available in supplements, with no evidence of harm.

Members therefore agreed that the information available at this time suggested that MSM was relatively safe and did not warrant scheduling. However, the data presented did not constitute a rigorous data package and Members agreed therefore that it would not be appropriate to include MSM in Appendix B. In addition, Members argued that some minor concerns regarding pregnancy and lactation risks, while not significant, were sufficient to preclude an Appendix B listing. A Member remained concerned that there was a lack of breast feeding and pregnancy warnings on the listed complementary medicines. Members agreed therefore to recommend that the delegate refer this to TGA for consideration.

Members agreed that there still remained a need to clarify the above intent with regard to the likely capture of MSM through the existing DMSO scheduling. A Member suggested that this could be achieved by limiting the DMSO entry to exclude derivatives of DMSO. Other Members, while agreeing that this would exempt MSM, were concerned that it would also exclude other possible derivatives when no information had been tabled as to the suitability of such a move. Members therefore agreed that the clearest approach was to specifically exempt MSM from the DMSO scheduling entries.

Members also discussed the appropriate terminology for any schedule reference to MSM and agreed that the AAN, dimethyl sulfone, should be used. Members additionally agreed that, for clarity, a cross reference should be added to the SUSMP index from methylsulfonylmethane to dimethyl sulfone.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the joint ACCS-ACMS were clear and appropriately supported. The delegate agreed with these recommendations. The

delegate also agreed that an early implementation period was appropriate to clarify the coverage of the current DMSO entries.

The delegate agreed that the relevant matters under section 52E (1) of the Act included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate decided to amend the Schedule 4 and Schedule 6 listing of dimethyl sulfoxide to specifically exclude dimethyl sulfone. The delegate also agreed to the addition of a cross reference in the SUSMP index from methylsulfonylmethane to dimethyl sulfone. The delegate decided that an implementation date of 1 September 2011 was appropriate (i.e. three months after publication of the final decision).

The delegate agreed to refer the issue of labelling of supplements containing dimethyl sulfone with pregnancy and breastfeeding warnings to the TGA for consideration.

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that dimethyl sulfoxide's Schedule 4 and Schedule 6 entry be amended to specifically exclude dimethyl sulfone. The delegate also confirmed the addition of a cross reference in the SUSMP index from methylsulfonylmethane to dimethyl sulfone. The delegate additionally confirmed an implementation date of 1 September 2011.

Schedule 4 – Amendment

DIMETHYL SULFOXIDE – Amend entry to read:

DIMETHYL SULFOXIDE (excluding dimethyl sulfone) for therapeutic use **except:**

(a) when included in Schedule 6; or

(b) in in vitro test kits.

Schedule 6 – Amendment

DIMETHYL SULFOXIDE – Amend entry to read:

DIMETHYL SULFOXIDE (excluding dimethyl sulfone):

(a) when not for therapeutic use; or

(b) for treatment of animals:

(i) when combined with no other therapeutic substance(s);

(ii) in liquid preparations containing copper salicylate and 1 per cent or less methyl salicylate as the only other therapeutic substances; or

(iii) in clay poultice containing 2 per cent or less of dimethyl sulfoxide.

PART B – FINAL DECISIONS ON MATTERS NOT REFERRED TO AN ADVISORY COMMITTEE

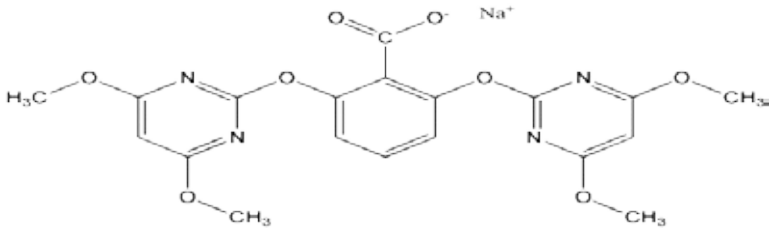
4. CHEMICALS

4.1 BISPYRIBAC

BACKGROUND

Bispyribac sodium is a post-emergence herbicide that inhibits the synthesis of key amino acids causing susceptible plants to stop growing and die within two to three weeks.

The IUPAC name for bispyribac sodium is sodium 2,6-bis[(4,6-dimethoxy-pyrimidin-2-yl)oxy]benzoate and the structure is:



XXXXX submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking the approval of a new technical grade active constituent (TGAC) bispyribac sodium and registration of the XXXXX.

The XXXXX Risk Assessment Technical Report on Sumitomo's APVMA submission included a scheduling recommendation for bispyribac sodium. The delegate agreed that this was a matter for a scheduling consideration. The delegate also decided that this matter did not require advice from the ACCS as the proposal was straight forward and the chemical had been subjected to the APVMA registration process. The delegate also indicated that the key data was robust, with a single clearly defined end point of concern with a simple proposed cut-off consideration, no apparent potential for requiring additional controls through SUSMP Appendices or for unintended regulatory impact.

SCHEDULING STATUS

Neither bispyribac sodium nor any other chemicals in this class (pyrimidinyloxybenzoic acids) appear to be currently scheduled.

SUBMISSIONS

Applicant's submission

The XXXXX Report proposed that, based on the hazard profile of bispyribac sodium as well as the product XXXXX, bispyribac sodium be included in Schedule 5 with a cut-off at 10 per cent or less for exemption from scheduling.

Other XXXXX conclusions included:

- There were no objections on human health grounds to approval of bispyribac sodium XXXXX.
- No ADI or ARfD have been established for bispyribac sodium because it was not intended for use in food producing agriculture.
- No re-entry or re-handling statements were required.
- No warning or precautionary statements were required.

Toxicology

The delegate noted the following toxicology summary for the TGAC bispyribac sodium:

XXXXX

- Bispyribac sodium was of low acute oral toxicity to XXXXX, and of low acute dermal and inhalational toxicity in XXXXX. The compound was non-irritating to the skin and slightly irritating to the eye of XXXXX and non-sensitising to the skin of XXXXX. XXXXX.
- Upon administration, bispyribac sodium was absorbed rapidly and completely. High levels of bispyribac sodium were found in plasma, liver, lung and gastrointestinal tract. The evaluator asserted that there was no evidence for bioaccumulation as administered bispyribac sodium was rapidly excreted in faeces and urine.
- XXXXX. The repeat-dose dermal study in XXXXX did not result in any systemic toxicity or other treatment related findings. XXXXX.
- There was no evidence of reproductive toxicity or developmental toxicity XXXXX. Further, no evidence of developmental toxicity was seen in XXXXX.
- Bispyribac sodium showed no evidence of carcinogenic or mutagenic, genotoxic potential. Additionally, three impurities and six metabolites tested negative for mutagenic potential.
- Bispyribac sodium was not tested for neurotoxicity. The evaluator, however, concluded that there was no evidence of neurotoxicity in any of the acute or repeat dose studies submitted.

Formulated Product

XXXXX

- The product XXXXX has a low acute toxicity profile. XXXXX. XXXXX was not a skin or eye irritant in rabbits, and was a non sensitiser in guinea pigs.
- The evaluator indicated that as the product was not an eye irritant in XXXXX, it was less toxic than that of the TGAC bispyribac sodium.

Exposure

- XXXXX.
- The potential routes of exposure to the product from XXXXX application are dermal, inhalational and possibly ocular.
- Workers using this product are likely to be the XXXXX. Given this, workers are likely to be exposed to this product infrequently on a short term basis.
- In view of the limited number of applications per year and the limited period for potential worker exposure, it was considered that a three week (21-day) dermal toxicity study in XXXXX with bispyribac sodium technical was the most relevant study available for use in the OH&S risk assessment of the product. A NOEL of 1000 mg/kg bw/d was identified in this study based on the lack of systemic toxicity or treatment related effects observed at the highest dose tested.

DELEGATE'S DISCUSSION

The delegate noted that bispyribac sodium had low acute toxicity via the oral, dermal and inhalation routes. It was, however, a slight eye irritant, but not a skin irritant and was not a skin sensitiser. Therefore bispyribac's toxicity profile aligned with the SPF factors for Schedule 5.

The delegate additionally noted that 10 per cent bispyribac sodium was not an eye irritant. The delegate therefore concluded that 10 per cent or less bispyribac sodium did not have any concerns that would warrant controls through scheduling. The delegate decided that preparations containing more than 10 per cent bispyribac should be listed in Schedule 5.

Additionally, the delegate agreed with the recent precedent to, where possible, schedule more generally rather than limit an entry to a specific salt, unless it is expected that the specific salt will have unique toxicity. As this was not the case for bispyribac sodium, the delegate decided that the schedule entry should be bispyribac, not bispyribac sodium.

The delegate also agreed that an implementation period of three months was appropriate.

The delegate agreed that the relevant matters under section 52E (1) of the Act included (a) risks and benefits; and (c) toxicity.

DELEGATE'S FINAL DECISION

That the delegate decided to include more than 10 per cent bispyribac in Schedule 5. The delegate also decided that an implementation date of 1 September 2011 was appropriate (i.e. three months after the publication of the final decision).

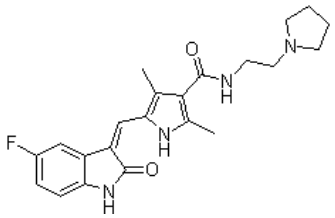
Schedule 5 – New entry

BISPYRIBAC **except** in preparations containing 10 per cent or less of bispyribac.

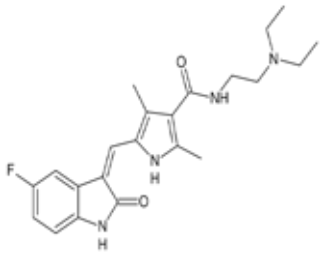
4.2 TOCERANIB

BACKGROUND

Toceranib is a tyrosine kinase inhibitor with an indolinone chemical structure. The same mode of action which leads to the anti-cancer effect of tyrosine kinase inhibitors also leads to a number of undesirable non-target biological effects, including toxicity in haematopoietic organs and the developing foetus. The IUPAC name for toceranib is toceranib phosphate and the structure is:



A structurally similar drug, sunitinib, was approved by the TGA for human therapeutic use. Sunitinib was listed in Schedule 4. The structure of sunitinib is:



XXXXX submitted data to the Australian Pesticides and Veterinary Medicines Authority (APVMA) seeking the approval of a new technical grade active constituent (TGAC) toceranib (as toceranib phosphate) XXXXX.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for toceranib. A delegate agreed that this was a matter for a scheduling consideration. The delegate decided that this matter did not require advice from the ACCS as the proposal was straight forward, the key data was robust, a similar substance, sunitinib, was already scheduled and there was no apparent potential for requiring additional controls through SUSMP Appendices or for unintended regulatory impact.

SCHEDULING STATUS

Toceranib was not currently specifically scheduled. Sunitinib (structurally similar to toceranib) was listed in Schedule 4 and was likely to capture toceranib as a derivative.

INITIAL SUBMISSIONS

Applicant's submission

The XXXXX Report recommended that, based on the use pattern XXXXX which requires veterinary diagnosis and management and the toxicological profile, toceranib should be included in Schedule 4.

Other evaluator conclusions included:

- There were no objections on human health grounds to the approval of toceranib (as tocenarib phosphate) XXXXX.
- No ADI or ARfD were established, as the product will not be used in food-producing animals.
- While the product was intended for use by professional users and domestic users when sold under prescription, the anticipated low exposure resulting from the use pattern XXXXX and the presentation as a XXXXX indicated that a NOAEL for occupational risk assessment and a quantitative assessment based on Margin of Exposure values was not required.
- The warning statements and general safety precautions recommended to the APVMA included:
  - *WARNING - Toceranib may cause birth defects. Women of child bearing age are advised not to administer this product.*
  - *Children and pregnant women should not come into contact with this drug. Keep children and pregnant women away from vomitus, faeces and urine of treated* XXXXX.

Toxicology

The delegate noted the following toxicology summary for the TGAC tocenarib:

XXXXX

- Toceranib had low acute oral toxicity in XXXXX.
- No reliable data was available to determine the dermal LD_{50}, though in XXXXX no deaths were seen following administration of XXXXX of the free base or the phosphate salt.

- XXXXX, toceranib free base was a slight irritant to eyes, while toceranib phosphate was a moderate eye irritant. Toceranib phosphate was non-irritating to XXXXX.
- No acute inhalational studies were submitted but given the acute toxicity profile of toceranib, it was considered unlikely to be of significant inhalation toxicity.
- None of the repeat oral studies in dogs established a NOAEL. The major target organs affected included bone marrow, pancreas, adrenals and reproductive organs (testes and ovaries). At higher doses toceranib also induced leukopoenia and effects on the gastrointestinal tract, lymph nodes and thymus. These effects are generally the expected consequences of inhibition of angiogenesis, haematopoietic differentiation and/or proliferation. In the only available sub-chronic oral study, the LOAEL was XXXXX for every other day dosing.
- No chronic or carcinogenicity studies were submitted. However, toceranib did not induce mutagenic or genotoxic effects in XXXXX. In an XXXXX test up to the limit dose a statistically significant dose-dependent increase in micronuclei were seen against concurrent controls. The statistically significant response in this limit dose study may not be biologically relevant and, overall the finding was considered equivocal (i.e. does not provide robust evidence that toceranib phosphate was an *in vivo* genotoxicant).
- No reproductive or developmental toxicity studies were submitted. However the applicant indicated that toceranib was likely to induce serious developmental effects including foetal resorptions and malformations, and supplied a published developmental study on the structurally related chemical, sunitinib which was foetotoxic and teratogenic in rats and rabbits at 5 mg/kg bw/d and above, and there was evidence of foetotoxicity at doses as low as 0.5 mg/kg bw/d in rats and 1 mg/kg bw/d in rabbits. The evaluator, however, argued that in the absence of historical control data the toxicological significance of these findings was unclear.
- Furthermore, sunitinib is listed by the TGA as Pregnancy Category D, which are "*Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage*." Thus, it was expected that adverse effects on pregnancy (e.g. resorptions and malformations) would be observed in teratogenicity studies in laboratory animals with toceranib.
- In the only available sub-chronic study, a XXXXX, small testes size and associated decreased mean absolute and relative testes weight, together with tubular vacuolation and germ cell depletion in the testes and a concurrent reduction of spermatoazoa in the epididymes were seen at XXXXX. with a reduced incidence of mature/regressing corpora lutea of the ovaries and an increased incidence of small follicles seen at XXXXX. This data from repeat dose studies was considered to provide sufficient evidence that toceranib be considered likely to have a reproductive toxicity potential.
- The evaluator indicated that although toceranib was of low acute toxicity (with the exception that toceranib phosphate was a moderate eye irritant), the available

information suggested that toceranib would be hazardous with repeated oral exposure and may be hazardous during pregnancy following a single exposure.

Toxicology - Formulated Product

- Based on the toxicity of all ingredients in the product, it was considered likely to have low acute oral, dermal and inhalation toxicity, slight eye irritation, non-irritating to the skin and not a skin sensitiser.
- Although the acute toxicity estimation indicated that the product would be considered a slight eye irritant, the presentation of the product XXXXX mitigates the risk of eye irritation. The evaluator further asserted that the proposed warning statements would address and mitigate any potential for ocular exposure (i.e. likelihood of eye irritation to the user was negligible).
- The applicant indicated that as the product is in the same anti-angiogenic class of anti-neoplastic agents that are known to increase embryolethality and foetal abnormalities, the product administration should be expected to result in adverse effects on pregnancy in XXXXX. Therefore the label states that the product is not to be used in pregnant or lactating XXXXX intended for breeding. In addition, as the product may impair male and female fertility and embryo/foetal development, the label cautions humans administering the drug against contact with tablets, faeces, urine and vomit of XXXXX. The label also cautions that pregnant women should not routinely administer the product; should avoid contact with faeces, urine and vomit from treated XXXXX.

<u>Public Exposure</u>

- XXXXX.
- The delegate noted that a European Medicines Agency's Committee for Medicinal Products for Veterinary Use Assessment Report indicated that "the finished product was initially intended to be packaged into HDPE bottles with polypropylene closures. The applicant, however, changed the primary package to XXXXX after a question was raised regarding the need for a more child resistant package due to the product's high toxicity". The delegate noted that such packaging issues were a matter for the regulator.
- XXXXX. The dosage given should be based on veterinary assessments conducted weekly for the first six weeks and thereafter, every six weeks.
- Administration of the product will primarily be conducted by members of the public. There will be opportunity for dermal, oral and accidental ocular exposure.
- Exposure to toceranib during dosing, however, was likely to be low. Administration of a XXXXX formulation to non-food-producing companion animals was a low exposure pattern, with only dermal exposure expected likely to occur. Additionally, the XXXXX, and any dermal exposure was likely to involve contact with the film coat rather than with the interior which contains toceranib. This presentation was

expected to effectively minimise toceranib exposure to the person administering the product. The delegate noted the evaluator's concern that the proposed draft label did not include any warning against splitting, breaking or crushing the XXXXX. This would increase the potential for dermal exposure.

- While exposure during dosing was likely to be negligible, there was an increased likelihood of exposure to small amounts of toceranib following dosing of XXXXX, via contact with XXXXX, or when cleaning vomitus or urine/faeces. Diarrhoea and vomiting are relatively common in XXXXX, and diarrhoea is one of the more common adverse reactions seen upon administration of the product.
- Exposure routes would primarily be dermal with a limited possibility of subsequent hand-to-mouth oral exposure and hand-to-eye exposure in adults. As it was expected that owners would take normal hygiene measures, it was likely that toceranib would only be in contact with the skin for a short period of time, which will limit the amount absorbed through the skin and possible oral and ocular exposure. Potential oral and ocular exposure was considered to be minimal.
- There was the possibility of a child ingesting a single misplaced XXXXX. There was also the unlikely possibility of a child ingesting an entire bottle of XXXXX within a child resistant bottle. Similarly, there was the unlikely possibility of a child ingesting an entire pack of XXXXX within child resistant packaging.
- There was also the possibility of child for dermal exposure to the product by accidental handling. Additionally, there was the possibility of a child having ocular exposure to the product from traces of product on hands being transferred to the eyes. The frequency of possible dermal and ocular exposure would be rare and the probability of dermal and ocular exposure to toceranib was low due to the formulation.

<u>Occupational Exposure</u>

- It is expected that most dosing of animals would be carried out by pet owners. There may be some exposure to staff working in veterinary practice or in animal boarding houses, and it was likely that this exposure would be similar to that described above for pet owners.

Hazard classification

- Toceranib was not listed on Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database.
- With the available toxicology information, the evaluator recommended classification of the active constituent toceranib as a hazardous substance according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following cut-off concentrations and risk phrases:

Conc. ≥25%	*"May cause harm to the unborn child", "Possible risk of impaired fertility", "Danger of serious damage to health by prolonged exposure if swallowed", "Harmful if swallowed"* and *"Irritating to eyes".*
Conc. ≥20% and <25%	*"May cause harm to the unborn child", "Possible risk of impaired fertility"* and *"Danger of serious damage to health by prolonged exposure if swallowed* and *"Irritating to eyes".*
Conc. ≥10% and <20%	*"May cause harm to the unborn child", "Possible risk of impaired fertility"* and *"Danger of serious damage to health by prolonged exposure if swallowed".*
Conc. ≥5% and <10%	*"May cause harm to the unborn child"* and *"Possible risk of impaired fertility* and *"Danger of serious damage to health by prolonged exposure if swallowed".*
Conc. ≥1% and <5%	*"May cause harm to the unborn child"* and *"Danger of serious damage to health by prolonged exposure if swallowed".*
Conc. ≥0.5% and <1%	*"May cause harm to the unborn child"*

DELEGATE'S DISCUSSION

The delegate agreed that the relevant matters under section 52E (1) of the Act included (a) risk and benefits; (b) purpose for use; and (c) toxicity.

Based on the need for a veterinarian to diagnose and manage treatment of the condition, the delegate decided that toceranib should be a Schedule 4 substance.

The delegate noted that while not specifically scheduled, toceranib was almost identical to sunitinib, both structurally and in its MOA. Toceranib would therefore probably be captured by the Schedule 4 sunitinb entry through SUSMP Part 1 (2)(C) i.e. an entry also captures "every salt, active principle or derivative of the substance …". However, for clarity and in line with recent practice, the delegate decided that a specific scheduling entry for toceranib was necessary.

Additionally, the delegate agreed with the recent precedent to, where possible, schedule more generally rather than limit an entry to a specific salt, unless it was expected that the specific salt will have unique toxicity. The delegate therefore decided that the Schedule 4 entry should be toceranib, not toceranib phosphate.

The delegate also noted that the available information suggested that toceranib may be hazardous during pregnancy. While no specific studies on developmental toxicity were submitted, it was reasonable to frame warning statements based on the inference that toceranib, as a member of the tyrosine kinase inhibitors, would be likely to pose such risks. The delegate concluded, however, that in the case of toceranib supplied by a

veterinarian the wording of such statements, and whether such warnings should also consider the potential for reproductive toxicity, was a matter for the regulator. The delegate confirmed that additional controls through an Appendix D listing were not necessary.

The delegate agreed that an implementation period of three months was appropriate.

DELEGATE'S FINAL DECISION

The delegate decided to include toceranib in Schedule 4. The delegate also decided that an implementation date of 1 September 2011 was appropriate (i.e. three months after the publication of the final decision).

Schedule 4 – New entry

TOCERANIB.

5. MEDICINES

5.1 APIXABAN

BACKGROUND

Apixaban is an anticoagulant substance being investigated in the prevention of venous thromboembolic events in patients undergoing elective total hip or knee replacement surgery. It is a Factor Xa inhibitor, in the same class as rivaroxaban.

SCHEDULING CONSIDERATION

The delegate noted that:

- As apixaban is not scheduled in Australia, this is a consideration of scheduling of a new chemical entity as outlined in the Scheduling Policy Framework (SPF). According to the SPF, the delegate may make a final decision on the scheduling of this substance without referring the matter to an advisory committee.
- The related substance, rivaroxaban is currently listed in Schedule 4.
- Apixaban is not currently scheduled in New Zealand.
- The seriousness of the indication mandates interaction with a medical professional.
- There is limited experience in the use of apixaban in the Australian environment. At this time apixaban has not been approved overseas, however the substance has received a positive opinion from the European Medicines Agency.
- Apixaban is not a narcotic, does not appear to produce dependency and does not appear to have a propensity for illicit use. There was no evidence to suggest abuse / misuse potential which would warrant a Schedule 8 entry.
- There was no evidence of sedation effects to warrant an Appendix K entry, nor pregnancy effects warranting an Appendix D entry.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits and (b) purpose for which the substance is to be used.

DELEGATE'S FINAL DECISION

The delegate decided to list apixaban in Schedule 4, effective 1 September 2011.

Schedule 4 – New Entry

APIXABAN.

5.2 CANAKINUMAB

BACKGROUND

Canakinumab is a recombinant human monoclonal interleukin-1β antibody used in the treatment of rare inherited auto-inflammatory disorders.

Canakinumab is captured by the Schedule 4 class entry for monoclonal antibodies.

A product containing canakinumab was registered by the TGA in December 2010. There is no evidence of use of canakinumab other than for human therapeutic use.

SCHEDULING STATUS

Canakinumab is not specifically scheduled, however is captured by the Schedule 4 class entry for monoclonal antibodies.

DELEGATE'S DISCUSSION

The delegate noted that a delegate may make a final decision on the scheduling of a substance which is not specifically scheduled without referring the matter to an advisory committee. The delegate agreed that this was a straightforward matter which did not require referral to an advisory committee.

At its November 2010 meeting, the New Zealand Medicines Classification Committee (MCC) recommended that the new substance canakinumab be classified as a prescription medicine.

The MCC noted that in New Zealand canakinumab was indicated for the treatment of Cryopyrin-Associated Periodic Syndromes, in adults and children aged four years and older including:

- Familial Cold Autoinflammatory Syndrome / Familial Cold Urticaria;
- Muckle-Wells Syndrome; and
- Neonatal-Onset Multisystem Inflammatory Disease / Chronic Infantile Neurological, Cutaneous Articular Syndrome.

The delegate noted that previously, the NDPSC and MCC have striven to maintain harmonisation of scheduling between Australia and New Zealand. However, the two Committees had in certain cases agreed not to harmonise and the initiation of a scheduling consideration to harmonise was at the discretion of a delegate.

There was no evidence suggesting abuse or misuse potential associated with canakinumab which would warrant restrictions greater than Schedule 4. There was also no evidence of sedation or teratogenicity effects which would warrant an Appendix D, K or L entry.

The delegate noted that although canakinumab was captured by the Schedule 4 class entry for monoclonal antibodies, including a specific Schedule 4 listing for canakinumab

would assist in the interpretation of scheduling by the jurisdictions. Apart from canakinumab and eculizumab (considered for scheduling separately at item 4.4), all other monoclonal antibodies currently registered by the TGA were separately listed (i.e. ofatumumab and rituximab).

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits and (f) other matters necessary to protect public health.

DELEGATE'S FINAL DECISION

The delegate decided to specifically list canakinumab in Schedule 4, with an implementation date of 1 September 2011.

Schedule 4 – New Entry

CANAKINUMAB.

5.3 ECULIZUMAB

BACKGROUND

Eculizumab is a recombinant humanised monoclonal antibody that acts as a complement blocker by inhibiting terminal complement activation at the C5 protein. It is used to reduce haemolysis in patients with paroxysmal nocturnal haemoglobinuria, a severe and disabling form of haemolytic anaemia.

A product containing eculizumab was registered by the TGA in 2009. There was no evidence of use of eculizumab other than for human therapeutic use.

SCHEDULING STATUS

Eculizumab is not specifically scheduled, however is captured by the Schedule 4 class entry for monoclonal antibodies.

DELEGATE'S DISCUSSION

The delegate noted that a delegate may make a final decision on the scheduling of a substance which is not specifically scheduled without referring the matter to an advisory committee. The delegate agreed that this was a straightforward matter which did not require referral to an advisory committee.

Eculizumab was approved by the US Food and Drug Administration as a prescription medicine in March 2007. Eculizumab is not scheduled in New Zealand.

According to the Martindale monograph for eculizumab, use of eculizumab increases susceptibility to meningococcal infections and patients should be monitored during treatment for early signs of meningococcal infections and treated as required. Susceptibility to other infections may also increase and eculizumab should be used with

caution in patients with systemic infection. Other adverse effects that have been reported with eculizumab include headache, nasopharyngitis, back pain, and nausea.

There was no evidence suggesting abuse or misuse potential associated with eculizumab which would warrant restrictions greater than Schedule 4. There was also no evidence of sedation or teratogenicity effects which would warrant an Appendix D, K or L entry.

The delegate noted that although eculizumab was captured by the Schedule 4 class entry for monoclonal antibodies, including a specific Schedule 4 listing for eculizumab would assist in the interpretation of scheduling by the jurisdictions. Apart from eculizumab and canakinumab (considered for scheduling separately at item 4.3), all other monoclonal antibodies currently registered by the TGA were separately listed (i.e. ofatumumab, rituximab).

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits and (f) other matters necessary to protect public health.

DELEGATE'S FINAL DECISION

The delegate decided to specifically list eculizumab in Schedule 4, with an implementation date of 1 September 2011.

Schedule 4 – New Entry

ECULIZUMAB.

5.4 FINGOLIMOD

BACKGROUND

Fingolimod is an immunomodulator indicated for the treatment of Multiple Sclerosis. Fingolimod is a prodrug, which after phosphorylation, acts as a sphingosine-1-phosphate receptor agonist that binds to the surface of lymphocytes and redirects them from the bloodstream and graft sites to the lymph nodes.

SCHEDULING CONSIDERATION

The delegate noted that:

- As fingolimod is not scheduled in Australia, this is a consideration of scheduling of a new chemical entity as outlined in the Scheduling Policy Framework (SPF). Fingolimod was first derived from an immunosuppressive natural product, myriocin, which was isolated from a type of entomopathogenic fungi (*Isaria sinclairii*) that was an eternal youth nostrum in traditional Chinese medicine. However, as deriving fingolimod from myriocin involves a series of significant chemical modifications, any entry for fingolimod would not inadvertently capture complementary use of *Isaria sinclairii*.

- Fingolimod is not currently scheduled in New Zealand.
- The seriousness of the indication mandates interaction with a medical professional and *adjunctive therapy.*
- There is limited experience in the use of fingolimod in the Australian environment.
- There is no evidence to suggest abuse / misuse potential which would warrant a Schedule 8 entry.
- There was no evidence of sedation effects which would warrant an Appendix K entry.
- Fingolimod is associated with teratogenicity affecting organogenesis and is listed as a Pregnancy Category D drug:
  "*Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*"
- Due to the seriousness of the indication treatment would always occur under the direction of a medical practitioner and an Appendix D entry would not be warranted.

Due to the potential for adverse pregnancy effects, the delegate decided to refer a proposal for an Appendix L entry for fingolimod to the Advisory Committee on Medicines Scheduling for advice.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits, (b) purpose for which the substance is to be used and (c) toxicity.

DELEGATE'S FINAL DECISION

The delegate decided to list fingolimod in Schedule 4, effective 1 September 2011.

Schedule 4 – New Entry

FINGOLIMOD.

5.5 TICAGRELOR

BACKGROUND

Ticagrelor is a reversible P2Y12 adenosine diphosphate (ADP) receptor antagonist under investigation for the reduction of major adverse cardiovascular events in patients with acute coronary syndrome.

SCHEDULING CONSIDERATION

The delegate noted that:

- As ticagrelor is not scheduled in Australia, this is a consideration of scheduling of a new chemical entity as outlined in section 4.2 of the Scheduling Policy Framework.

- Ticagrelor is not currently scheduled in New Zealand.
- Substances with similar properties (clopidogrel, prasugrel and ticlopidine) are listed in Schedule 4.
- Ticagrelor was approved as a prescription medicine by the European Medicines Agency on 3 December 2010.
- The seriousness of the indication mandates interaction with a medical professional and adjunctive therapy.
- There is limited experience in the use of ticagrelor in the Australian environment.
- There is no evidence to suggest abuse / misuse potential which would warrant a Schedule 8 entry.
- There was no evidence of effects in pregnancy or sedation which would warrant an Appendix D or Appendix K entry.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the substance and (b) purpose for which the substance is to be used.

DECISION

The delegate decided to list ticagrelor in Schedule 4, effective 1 September 2011.

Schedule 4 – New Entry

TICAGRELOR.

5.6 VERNAKALANT

BACKGROUND

Vernakalant is an antiarrhythmic under investigation as the hydrochloride for the treatment of atrial arrhythmias.

SCHEDULING CONSIDERATION

The delegate noted that:

- As vernakalant is not scheduled in Australia, this is a consideration of scheduling of a new chemical entity as outlined in the Scheduling Policy Framework (SPF). The delegate may make a final decision on the scheduling of this substance without referring the matter to an advisory committee.
- The seriousness of the indication mandates interaction with a medical professional. Vernakalant is only to be administered by intravenous infusion in highly-specialised hospital settings, e.g. Coronary Care Units and under the supervision of a cardiologist.

- There is limited experience in the use of vernakalant in the Australian environment. Vernakalant is listed as a prescription medicine in New Zealand. It has also been approved as a prescription medicine in the EU, indicated for rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults. Vernakalant is being evaluated in the USA.
- Vernakalant does not appear to have a propensity for illicit use. There was no evidence to suggest abuse / misuse potential which would warrant a Schedule 8 entry.
- Vernakalant can, in certain cases, produce a marked hypotensive response and hence is intended to be administered only in an intensive-care type setting under continuous ECG monitoring.
- Vernakalant is contraindicated in patients with severe aortic stenosis (narrowing of the aorta), low systolic blood pressure, advanced heart failure, some types of altered electrical activity in the heart or a very slow heart rate. It must also not be given to patients within four hours of intravenous treatment with class I and III anti-arrhythmics or within 30 days of having acute coronary syndrome.
- The proposed pregnancy category for vernakalant is B3:
  Drugs which have been taken only by 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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
- With respect to reproduction, no effects on pregnancy, embryofoetal development, parturition or post-natal development were observed after IV administration of vernakalant at exposure levels similar to or below the human exposure levels achieved after a single IV dose of vernakalant. In embryofoetal development studies with oral administration of vernakalant twice daily, malformations occurred XXXXX and to a certain extent XXXXX.
- In Europe, the Summary of Product Characteristics stated that "as a precautionary measure, it is preferable to avoid the use of vernakalant during pregnancy", however it was not specifically contra-indicated. It is likely that in Australia it would be recommended that the drug not be used in pregnancy. Given that the IV drug was indicated for single use inclusion in Appendix D was not necessary at this time. However, this situation may change if other formulations of vernakalant were to be developed and clinically trialled.
- There was no evidence of sedation effects which would warrant an Appendix K entry.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits, (b) purpose for which the substance is to be used and (c) toxicity

DELEGATE'S FINAL DECISION

The delegate decided to include vernakalant in Schedule 4, with an implementation date of 1 September 2011.

Schedule 4 – New Entry

VERNAKALANT.

6. EDITORIALS AND ERRATA

Amorolfine - Errata

In December 2010 XXXXX noted that amorolfine was listed in Appendix H even though it was no longer included in Schedule 3.

The delegate noted that in June 2010 the NDPSC agreed to reschedule all amorolfine topical preparations from Schedule 3 to Schedule 2. As part of this rescheduling the Appendix H entry should have been removed as Schedule 2 substances are allowed to be advertised.

Mercurochrome - Editorial

Following publication of the March 2011 delegate's final decision to include mercurochrome in Schedule 2 and 4 the Secretariat received a request from XXXXX to editorially amend the entries to avoid possible confusion with the Schedule 6 entry.

The current scheduling of mercurochrome stated:

> **Schedule 2**
>
> MERCUROCHROME in preparations for external use containing 2 per cent or less of mercurochrome.
>
> **Schedule 4**
>
> MERCUROCHROME **except** when included in Schedule 2 or 6.
>
> **Schedule 6**
>
> MERCUROCHROME for the treatment of animals, in preparations for topical use.

The request suggested that inclusion of "except when included in Schedule 6" in the Schedule 2 entry would reduce confusion in interpretation (i.e. there was potential to interpret the current Schedule 2 and 6 wording such that an external topical animal preparation containing 2 per cent or less mercurochrome would be captured by both entries).

The delegate noted that this request aligned with the intent of the March 2011 final decision where the decision did not intend for the newly created Schedule 2 entry to override the existing Schedule 6 entry.

Praziquantel - Errata

The ACCS recently noted that praziquantel was included in Appendix B as well as in Schedule 4 for human therapeutic use.

The delegate noted that if a substance was included in Appendix B then it did not require controls by scheduling and could not be included in any other Schedule. If that substance

was listed in another schedule, this indicated that controls through scheduling were required and it could not be listed in Appendix B.

As the Schedule 4 praziquantel entry specified human therapeutic use only, this already indicated that all other uses were unscheduled.

The delegate noted that this errata could be resolved by removing the praziquantel entry from Appendix B. Such a decision would not impact the scheduling status of praziquantel or its enforcement (either for human therapeutic or other uses), however would better align with the overall intent of Appendix B.

Praziquantel scheduling history

Praziquantel was included in Schedule 4 for all uses in June 1976. In May 1977 the NDPSC agreed to delete the Schedule 4 entry and exempt praziquantel from scheduling. The minutes stated that the only reason it was initially included in Schedule 4 was to control its use during the development of a national program for the control of cestocides.

Praziquantel was included in Appendix B in the early 1980s (noting that at that time the purpose of Appendix B differed from its current functions). In February 1989 this Appendix B entry was deleted and a new Schedule 4 entry was included for praziquantel for human therapeutic use.

In May 1995, the NDPSC confirmed that on the basis of its low toxicity praziquantel should remain unscheduled for animal use.

In October 2005, the NDPSC agreed to include praziquantel in Appendix B for animal use, noting its low toxicity. This decision resulted in no regulatory change as animal use was already unscheduled and appeared to have inadvertently been made, incorrectly assuming that an Appendix B entry could be made for a particular use.

Appendix B history

Appendix B was introduced to provide a historical record of those substances which have been actively considered to not require scheduling. Appendix B can be used by regulators to determine whether to seek a scheduling consideration of a substance, noting that the substance had previously been considered.

It is recognised that an Appendix B listing was limited by the information available at the time of consideration. An Appendix B entry therefore also includes information on the date of listing, reason for listing and the main use pattern that was known at the time of listing (area of use).

DELEGATE'S FINAL DECISION

The delegate decided to editorially amend Appendix H by removing the amorolfine entry.

The delegate also decided to editorially amend the Schedule 2 mercurochrome entry by including the words "except when included in Schedule 6".

The delegate decided to editorially amend Appendix B by removing the praziquantel entry.

The delegate decided on an implementation date of 1 September 2011 (earliest possible implementation date) for the all of the above editorial amendments.

Schedule 2 – Amendment

MERCUROCHROME – Amend entry to read:

MERCUROCHROME in preparations for external use containing 2 per cent or less of mercurochrome **except** when included in Schedule 6.

Appendix B – Amendment

Praziquantel – delete entry.

Appendix H – Amendment

Amorolfine – delete entry.