Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

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

DECEMBER 2011 INVITATION FOR FURTHER SUBMISSIONS

Notice under subsection 42ZCZP of the Therapeutic Goods Regulations 1990

A delegate of the Secretary to the Department of Health and Ageing hereby gives notice of delegates' interim decisions under subsection 42ZCZP of the Therapeutic Goods Regulations 1990 (the Regulations).

This notice provides the interim decisions of delegates, the reasons for those decisions and invites further submissions from the applicant and parties who made a valid submission in response to the original invitation for submissions (published on 10 August 2011 at www.tga.gov.au/newsroom/consult-scheduling-acms-1110.htm). Edited versions of these submissions are available at www.tga.gov.au/industry/scheduling-submissions.htm.

Further submissions must be relevant to the proposed amendment, must address a matter mentioned in section 52E of the *Therapeutic Goods Act 1989* and be received by the closing date (**13 January 2012**).

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.

Please note that all valid submissions received on or before the closing date will be published following removal of confidential information. It is up to the person making the submission to highlight any information which they wish to be considered as confidential. Material claimed to be commercial-in-confidence will be considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework (SPF), issued by the National Coordinating Committee on Therapeutic Goods. The SPF is accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Persons making submissions are strongly encouraged to lodge submissions in electronic format (word or unsecured PDF preferred) via the email address provided below. Submissions, preferably in electronic format, should be made to:

Medicines and Poisons Scheduling Secretariat (MDP88)
GPO Box 9848
CANBERRA ACT 2601
e-mail SMP@health.gov.au Facsimile 02-6289 2650

The closing date for further submissions is **13 January 2011**.

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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])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	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 [ACSOM])
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
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority (NZ)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
HCN	Health Communication Network
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 [ACNM])
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No Observed Adverse Effect Level
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health
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

INTERIM DECISIONS ON PROPOSALS REFERRED TO AN ADVISORY COMMITTEE

1. OCTOBER 2011 MEETING OF THE ADVISORY COMMITTEE ON CHEMICALS SCHEDULING (ACCS) – ACCS#3

1.1 AMETOCTRADIN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Ametoctradin – seeking advice on a proposal to create a new Appendix B entry. Advice is also sought on alternatively including ametoctradin in Schedule 5.

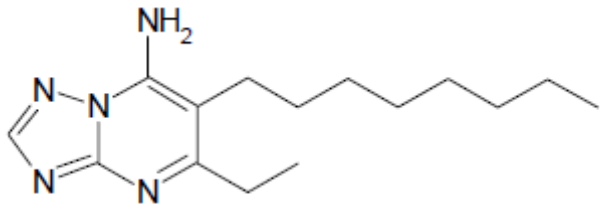
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that an Appendix B entry be created for ametoctradin. The Committee also recommended an implementation date of no more than six months after the delegate's final decision (i.e. May 2012).

BACKGROUND

Ametoctradin belongs to the trazolopyrimidylamines class of chemicals. It controls major plant pathogens from the Oomycete class of fungi, specifically downy mildews and *Phytophthora spp*. on vine, vegetable crops and ornamentals. Ametoctradin prevents disease by inhibiting the infectious stages of the pathogen, through direct effects on the germinations of sporangia. It has shown to be active against zoospores and zoosporangia by inhibiting mitochondrial respiration in complex III, and, thus, preventing zoospore formation, release and motility.

The IUPAC name for ametoctradin is 5-ethyl-6-octyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine and the structure is:



XXXXX has submitted data to the APVMA seeking approval of the active constituent ametoctradin, and registration of a new product XXXXX.

A toxicology assessment of ametoctradin has been conducted jointly by scientists from XXXXX

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission, which picked up the information from the joint international assessment, included a scheduling recommendation for ametoctradin. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was required.

SCHEDULING STATUS

Ametoctradin is not currently specifically scheduled. The Secretariat was unable to locate any current entry that would capture ametoctradin as a derivative nor any group entry that would capture ametoctradin.

INITIAL SUBMISSIONS

Applicant's submission

The XXXXX Risk Assessment Technical Report on XXXXX APVMA submission recommended that, based on the toxicity profile, ametoctradin be listed in Appendix B. The delegate noted that although the toxicity profile of ametoctradin appeared be consistent with an Appendix B listing, the delegate sought the views of the Committee on whether there were any specific grounds that might instead warrant a Schedule 5 listing.

Other evaluator's conclusions included:

- There were no objections on human health grounds to the approval of ametoctradin or the registration of the product containing XXXXX of ametoctradin.
- The ADI for ametoctradin was established at XXXXX based on the overall lack of adverse toxicological effects of ametoctradin across the repeat-dose toxicology data set at close to or above the limit-dose of XXXXX and using a 100-fold safety factor.
- An acute reference dose (ARfD) was not proposed for ametoctradin, as it was considered unlikely to present an acute hazard to humans after a single dose administration.

Toxicology

Members noted the following toxicology summary for the technical grade active constituent ametoctradin:

XXXXX

- Ametoctradin had a low acute oral XXXXX dermal XXXXX and inhalational toxicity XXXXX in XXXXX. Ametoctradin was non-irritating to the skin and eye of XXXXX, and non-sensitising in a XXXXX.
- The Committee considered the delegate's comments regarding whether the low mammalian toxicity and the proposed mechanism of action (inhibition of

mitochondrial respiration in Complex III) was consistent with the low mammalian toxicity, or whether low systemic toxicity was more consistent with poor bioavailability by the oral route. Members noted that the evaluation report contained some basic information regarding these issues as described below.

- *Mitochondrial respiration in Complex III*: Ametoctradin prevents disease by inhibiting the infectious stages of the pathogen, through direct effects on the germinations of sporangia. It had shown to be active against zoospores and zoosporangia by inhibiting mitochondrial respiration in Complex III, and, therefore preventing zoospore formation, release and motility.

- *Oral toxicity*: In an acute oral toxicity study XXXXX were orally administered with XXXXX of ametoctradin. No mortality occurred and no clinical signs were observed during the study period. No macroscopic pathologic abnormalities were noted in the animals examined at the end of the observation period.

- Ametoctradin was rapidly absorbed when administered as a single dose in XXXXX. There was no evidence of significant tissue accumulation even following repeated high doses.

- Ametoctradin was not carcinogenic or genotoxic. Ametoctradin was not a reproductive toxicant in XXXXX, nor a developmental toxicant in XXXXX at the limit dose of XXXXX.

- No evidence of neurotoxicity was recorded in acute or subchronic-duration studies at the limit dose, and ametoctradin was not immunotoxic in a short-term study exceeding the limit dose.

- Toxicological studies on three major metabolites indicated they were not potential mutagens, genotoxins and/or had low oral repeat dose toxicity.

- The evaluator indicated that ametoctradin was of low toxicity in repeat dose studies in animals with all studies failing to elicit adverse signs of toxicity at close to or in excess of the limit dose of XXXXX and concluded that based on its toxicity profile in experimental animals, ametoctradin was unlikely to cause significant toxicological harm to humans.

Hazard classification

- The evaluator noted that ametoctradin was not listed on Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2011). Based on the toxicological profile of ametoctradin, the evaluator concluded that it would not be classified as a hazardous substance in accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Product XXXXX

- Members noted the following toxicology data for the product containing XXXXX ametoctradin. The product, in addition to ametoctradin, also contains XXXXX.

  XXXXX

- Based on the findings of the toxicological studies evaluated, the product had low acute oral, dermal and inhalational toxicity in XXXXX. It was not a skin or eye irritant in XXXXX, and not a skin sensitiser in XXXXX.
- The Committee considered the delegate's comments regarding the broad range of acute oral toxicity for the product and questioned whether this was the result of the acute toxicity profile of XXXXX which had an oral LD_{50} of XXXXX or whether this was due to the synergistic effect as a result of combining the two XXXXX. Members noted that the evaluation report had some information regarding acute oral toxicity of the product (described below) and there was no information on synergism or the reason for the broad acute toxicity range.
- In an acute oral toxicity study groups of XXXXX were administered with XXXXX of the product. On the first day of study, XXXXX animal of the first and XXXXX animals of the second XXXXX group died. Clinical signs in XXXXX revealed impaired and poor general state, dyspnoea, apathy, abdominal and lateral position, staggering, ataxia, atonia, absent pain reflex, piloerection, exsiccosis, salivation, lacrimation, chromodacryorrhoea, red clammy snout and reduced faeces. These were observed XXXXX after administration. Clinical signs administered with XXXXX were confined to impaired general state, dyspnoea and piloerection, which were observed from XXXXX after administration. The gross necropsy on XXXXX animals administered with XXXXX which died during XXXXX showed XXXXX black erosions/ulcers (1 mm diameter) of the glandular stomach, and one of the XXXXX additionally showed brown and pale discolouration of the liver. No macroscopic pathologic abnormalities were noted in the other XXXXX animals that died in the XXXXX groups, in the surviving animals of the XXXXX groups and in the animals of the XXXXX group examined at termination of the study.
- XXXXX
- XXXXX.

Exposure

- XXXXX
- The applicant had indicated that application to XXXXX may be made using dilute or concentrate spraying with XXXXX application methods. The proposed maximum rate of application is XXXXX, in a proposed dilute spray volume of XXXXX, or a minimum spray volume of XXXXX for concentrate spraying.

- No domestic use of the product was expected.
- Farmers XXXXX and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application with spray equipment, and cleaning up spills and equipment. The main route of exposure to the product and the spray will be dermal contact, with inhalation and ocular exposure to the dilute spray also expected.

XXXXX

- Since the NOEL will usually be derived from animal toxicity testing a margin of exposure (MOE) of 100 or above are usually considered to be acceptable, and was considered to be the case in this instance. The MOE takes into account both interspecies extrapolation and intraspecies variability.
- The evaluator noted that a variety of post-application activities will be carried out, including high to very high exposure activities such as harvesting by hand, XXXXX, bird control, XXXXX and scouting, as well as low-exposure activities such as irrigation, mechanical weeding and transplanting. The evaluator indicated that these risks can be mitigated with the following re-entry statements:
- For low- and medium-exposure activities such as irrigation, hand weeding and scouting:
  - *"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"*.
- For high-exposure activities such as harvesting by hand, pruning, XXXXX and XXXXX:
  - *"DO NOT allow entry into treated areas for seven days after application, 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"*.
- For very high-exposure activities such as XXXXX
  - *"DO NOT allow entry into treated areas for thirteen days after application, 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"*.

XXXXX

Applicant's Response to the Evaluation Report

The Scheduling Secretariat has been advised that XXXXX has considered the evaluation Report, including the scheduling recommendation, and advised that they agreed with the evaluator's scheduling recommendations.

October 2011 Pre-meeting Submissions

Two pre-meeting submissions XXXXX were received.

XXXXX supported the evaluator's recommendation i.e. inclusion of ametoctradin in Appendix B.

XXXXX did not state a position with regard to the delegate's scheduling proposal, but did make several specific comments in relation to 52E matters:

Risks and benefits

- Noted that ametoctradin could be used to manage disease resistance. Argued that repeated use of a chemical may lead pathogens to develop resistance against the chemical rapidly. Asserted that disease resistance could be delayed by mixing ametoctradin with other existing chemicals (two modes of acting chemicals in a combined spray). The submission argued that this approach would increase the longevity of several other chemicals and was a valuable tool in the disease management process.

Extent and pattern of use

- The product would control Oomycetes and it was also a mitochondrial respiration inhibitor. Also noted that they were investigating ametoctradin for use as a protectant fungicide in XXXXX.

Purpose

- Indicated that as a protectant fungicide, not a curative fungicide, it should be used before the disease infests the crop.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members 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; (c) toxicity; and (d) the dosage, formulation, packaging and presentation.

The Committee generally agreed that ametoctradin had a low acute toxicity profile and discussed whether an Appendix B or Schedule 5 listing was warranted.

Some Members noted that several countries, including the US and Canada, had already approved ametoctradin for domestic use. A Member noted the ametoctradin evaluation

reflected a joint global evaluation, and therefore asserted that, for consistency and in line with the evaluating countries decision, an Appendix B listing for ametoctradin was appropriate. Another Member noted, however, that the Appendix B recommendation was an Australian specific matter, and that it was inaccurate to imply that the joint global evaluation had endorsed this position. A Member also argued that, as MOE values were high the risks associated with exposure and resulting adverse effects would be minimal.

The Committee then discussed whether there was any issue arising from ametoctradin's mechanism of action that might require a Schedule 5 rather than Appendix B listing. Some Members were concerned that there was limited information in the evaluation report regarding the mechanism of action on the mitochondrial respiration in complex III. A Member, however, indicated that although the complex III was part of the mammalian mitochondrial respiratory chain, this was not a concern as there was no evidence to support the effects of ametoctradin in complex III of humans.

A Member raised concerns that although the evaluation report recommended an Appendix B listing for ametoctradin, several label warning statements, including re-entry statements, had been recommended. The Member argued that as Appendix B substances are usually considered sufficiently safe as to not require control by scheduling, the apparent need for label warning statements would send mixed messages to the public. Another Member asserted that as the product contains XXXXX, in addition to ametoctradin, it was appropriate for the evaluator to recommend these label warnings, based on the toxicity of XXXXX. The Member further indicated that a number of the label warning statements appeared to arise out of promoting good occupational practice, such as reducing exposure, rather than due to any particular toxicity concern. Members were also reassured that Appendix B substances were still subject to the APVMA registration process.

Regarding the product's broad acute toxicity range, the Members noted that there was limited information available in the evaluation report. A Member indicated that the product's broad acute toxicity would probably be due to the addition of XXXXX. Another Member questioned whether the broad acute toxicity was due to synergism, some Members, however, indicated that there was not sufficient evidence for synergism. Members generally agreed that the broad toxicity range probably was due to the combined toxicity of ametoctradin and XXXXX and was an issue for the product approval process, not scheduling.

A Member noted that although ametoctradin had low acute toxicity potential, it remains in the environment for a long duration. Another Member, however, asserted, and the Committee agreed that this was not a scheduling issue and would be dealt with through the separate regulatory mechanism for environmental concerns.

Other issues

Several Members raised concerns regarding the animal acute toxicity study methodology used in the assessment, including limited number of animals XXXXX exposed, and

indicated that such changes to methodology introduced greater uncertainty regarding the toxicity end-points. Some Members asserted that due to this lack of experimental vigour, a conservative approach must be taken. Members were, however, informed that the experimental methodology employed in these studies were conducted in accordance with the OECD Guideline for Testing of Chemicals (OECD/OCDE 423) (available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECD_GL423.pdf).

Implementation

A Member noted that ametoctradin is a new active, XXXXX. The Committee agreed that there were no matters requiring a delayed implementation period and an early implementation date for the scheduling was supported.

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 also agreed that an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012) was appropriate.

The relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits of the substance and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate decided to create an Appendix B entry for ametoctradin. The delegate also decided an implementation date of no more than six months after the delegate's final decision (i.e. May 2012).

Appendix B – New entry

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
AMETOCTRADIN	May 2012	a	1.3

1.2 DELTAMETHRIN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Deltamethrin – seeking advice on a proposal to reschedule deltamethrin, when impregnated in plastic resin strip material containing 4 per cent or less of deltamethrin, from Schedule 7 to Schedule 5.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

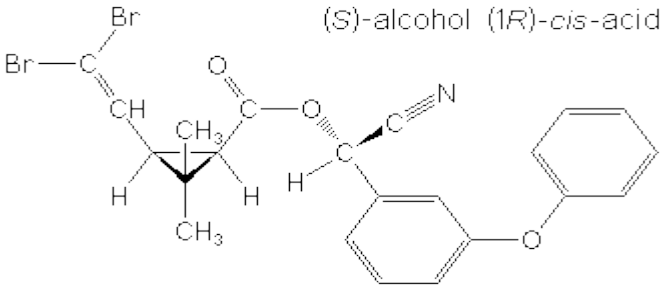
The Committee recommended that deltamethrin, when impregnated in plastic resin strip material containing 4 per cent or less, be rescheduled from Schedule 7 to Schedule 5. The Committee recommended an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

The Committee also recommended that the delegate communicate Member's concerns, to APVMA, regarding inclusion of appropriate label warning statements on the proposed product similar to that of the EU label warning statements.

BACKGROUND

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

The IUPAC name of deltamethrin is (S)-a-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate and the structure is:



Deltamethrin, a fourth generation pyrethroid, is highly resistant to exposure to sunlight and air. Because it is stable in the environment, deltamethrin may be carried by water or air to areas where the compound may endanger non-target species such as birds, reptiles, fish and plankton. Deltamethrin products are registered for use in Australia, and many other countries. However, Denmark has banned the outdoor use of deltamethrin products, due to concerns for the safety of the environment.

XXXXX had submitted data to the APVMA to register a new plastic deltamethrin product, XXXXX

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

Previous considerations on deltamethrin

In February 1979, the Poison Scheduling (Standing) Committee (PSSC) agreed to list decamethrin (a synonym of deltamethrin) in Schedule 6. In May 1979 the PSSC up scheduled decamethrin to Schedule 7.

In November 1988, the Drugs and Poisons Scheduling Committee considered scheduling of an aqueous suspension formulation, resulting in a Schedule 5 entry for 1 per cent deltamethrin, when formulated with no organic solvent other than glycol.

In February 1993, the NDPSC considered the scheduling of a 2.5 per cent deltamethrin formulation and agreed that this should be captured in Schedule 6.

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

In October 2004, the NDPSC agreed to reschedule 25 per cent deltamethrin when formulated as water dispersible granules, from Schedule 6 to Schedule 5.

In June 2008, the NDPSC decided to expand the Schedule 5 deltamethrin listing for aqueous preparations (when no organic solvent other than a glycol is present) from 1 per cent to 5 per cent.

In February 2010, the NDPSC considered a request to reschedule low concentration deltamethrin products and agreed to exempt products containing 0.1 per cent deltamethrin from scheduling.

SCHEDULING STATUS

Currently, deltamethrin is listed in Schedules 5, 6 and 7 depending on concentration and formulation, with an exemption from scheduling when in preparations containing 0.1 per cent or less of deltamethrin.

INITIAL SUBMISSIONS

Applicant's submission

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission recommended that the Schedule 5 deltamethrin entry be expanded to capture deltamethrin

when impregnated in plastic resin strip material containing 4 per cent or less of deltamethrin.

Other evaluator conclusions included:

- There were no objections on human health grounds to the registration of the products containing XXXXX of deltamethrin.
- The ADI of 0.01 mg/kg bw for deltamethrin was established in 1980 based on a NOEL of XXXXX using a 100-fold safety factor.
- No ARfD has been established for deltamethrin and no data were submitted to enable an ARfD to be set.

Toxicology - deltamethrin

Members noted that no acute toxicity studies on deltamethrin had been submitted. The data package comprised of five acute toxicology studies, including the release and diffusion of deltamethrin from the XXXXX, a study of the level of deltamethrin in plasma and the tolerance of the product by XXXXX. The studies were conducted with the product itself. A recent Periodic Safety Update Report (PSUR) was also included for the product which was currently marketed in Europe. The acute toxicity information for the active, as summarised below, was therefore taken from the previous XXXXX assessments.

Acute toxicity

- The acute oral LD_{50} was XXXXX and XXXXX. Members noted that according to the Scheduling Policy Framework (SPF), these toxicity end-points aligned with the Schedule 6 and Schedule 7 factors, respectively. XXXXX, the LD_{50} was greater than XXXXX.
- The dermal LD_{50} XXXXX was greater than XXXXX when applied as a XXXXX. The LC_{50} (4 h, aerosol) XXXXX was XXXXX.
- Toxic symptoms include muscular contractions, piloerection, respiratory defects, convulsions and hind quarters paralysis. Toxicity in XXXXX varied, depending on the carrier vehicle.
- Deltamethrin was not an irritant to XXXXX skin and was a mild eye irritant XXXXX. It was not a skin sensitiser XXXXX.

Subchronic toxicity

- Subchronic studies performed XXXXX resulted in decreases XXXXX bodyweight at XXXXX, with no pathological changes. Studies XXXXX, at doses up to XXXXX by gavage XXXXX, resulted in decreases in weight gain and the occurrence of liquid faeces in all treatment groups. CNS effects were seen at the high dose level only.

Depression of the patellar reflex was observed at XXXXX. Histopathological examination was unremarkable.

Chronic toxicity

- Chronic studies were performed XXXXX. XXXXX, there was no effect on behaviour, bodyweight, or on biochemical, haematological or urinanalytical parameters. There was no increase in tumour incidence. Histopathology was unremarkable. The NOEL was above XXXXX, there was no change in behaviour, and a small decrease in bodyweight gain at the high dose level. There were no significant changes in biochemical or haematological parameters. Pathological examination revealed a slightly increased incidence of axonal degeneration in nerves XXXXX. There was an apparent increase in interstitial adenomas in the testes of high dose males. The NOEL was XXXXX, there were no clinical signs of toxicity nor any decrease of bodyweight gain. Biochemical and haematological parameters were normal. Histopathology was unremarkable. The NOEL was above XXXXX.
- In a 3-generation reproduction study XXXXX there were no clinical signs of toxicity in the parents although there was a decrease in bodyweight at the high dose level. There was no change in fertility, gestation length, lactation, viability or litter size. XXXXX bodyweight was somewhat lower at the high dose level. Histopathology of XXXXX was unremarkable.
- Teratology studies have been performed XXXXX. In two studies XXXXX, at doses XXXXX respectively, maternal toxicity was observed particularly at the high dose level. There was no effect on implantation sites, foetal weight, or number of ossification sites. There was a significant increase in the number of supernumerary ribs. There was no increase in skeletal or visceral abnormalities. XXXXX, there was a dose-related decrease in maternal bodyweight gain. There was no effect on implantation sites, foetal weight, or number of ossification centres. There was no increase in skeletal or visceral abnormalities but delayed ossification was seen XXXXX. XXXXX, at doses up to XXXXX, there was a slight reduction in maternal bodyweight gain at the high dose level and also a decrease in foetal bodyweight at this dose level. There was no treatment-related increase in skeletal or visceral abnormalities.

Other toxicity issues

- A number of genotoxicity tests have been performed with deltamethrin. Negative results have been obtained in reverse mutation assays in XXXXX There was no increase in chromosome aberrations or sister-chromatid exchanges (SCE) in XXXXX. There was no increase in micronuclei or in chromosome aberrations in XXXXX following *in vivo* treatment at XXXXX. The dominant lethal assay in XXXXX was negative.
- In a neurotoxicity study XXXXX, deltamethrin at single doses up to XXXXX induced no clinical, macroscopic or histological signs of delayed neurotoxicity.

- Clinical observations of production workers and of agricultural workers had indicated that deltamethrin was irritating to skin and mucous membranes. Initial lesions were tenacious and painful pruritus (prickling sensation), followed by a blotchy burning sensation with blotchy erythema. The effects lasted for several days. The irritant effects may have been enhanced by the aromatic solvents in an emulsifiable concentrate formulation.

Hazard classification - deltamethrin

- The active constituent deltamethrin is listed in Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2010) with the following risk phrases for Conc. ³ 25% (T; R23/25) and 3% < Conc. <25% (Xn; R20/22) deltamethrin respectively:

T; R23/25:	Toxic by inhalation or if swallowed

Xn; R20/22	Harmful by inhalation and if swallowed

Toxicology – product XXXXX

Members noted the toxicology of the XXXXX deltamethrin, XXXXX

XXXXX

- The product had low acute oral and dermal toxicity and was non-irritant to the skin and not a skin sensitiser. The product had a slight eye irritancy potential with minimal to slight corneal involvement.
- An acute dermal toxicity study conducted XXXXX with a concentration of XXXXX, resulted in no unscheduled deaths. Body weight was unaffected by administration of the test material. All animals appeared normal for the duration of the study. The gross necropsies conducted at the termination of the study revealed no observable abnormalities.

Product eye irritation:

- In an eye irritation study, XXXXX were exposed to XXXXX of deltamethrin XXXXX. The eyes were either washed (for one min, 30 sec after the treatment) or not washed after treatment. At XXXXX after treatment positive fluorescein staining occurred in XXXXX eyes for the non-washed eyes. No positive staining occurred in any eyes XXXXX after treatment. Conjunctival irritation was clear by XXXXX The evaluator noted that these symptoms were considered as 'minimally irritating'.

Specific issue flagged by the delegate

The delegate noted that the toxicity profile of the powdered XXXXX appeared consistent with a Schedule 5 listing, based on the results of toxicity end-points of slight eye

irritation (both the powdered XXXXX and active ingredient) on animals. The delegate, however, noted that clinical studies on workers exposed to deltamethrin suggested different toxicity end-points for skin and eye irritancy than those derived from animal studies i.e. animal studies on the active showed it was non-irritant to skin and a mild irritant to eyes yet clinical observations of production workers and of agricultural workers have indicated that deltamethrin was irritating to skin and mucous membranes. Initial lesions were tenacious and painful pruritus (prickling sensation), followed by a blotchy burning sensation with blotchy erythema. The effects lasted for several days. The delegate therefore questioned whether the irritancy potential of XXXXX deltamethrin in the product may be greater than indicated by the animal studies. Members noted that the more severe irritant effects in the clinical studies may have been due to the solvents in the particular formulation (emulsifiable concentration) and that such matters are usually left for consideration during the product registration process.

PSUR

- A PSUR for the product XXXXX was produced using data from XXXXX.
- Regulatory action was taken on the basis of pharmacovigilance reports within the cover period of the PSUR. In France, the summary of product characteristics (SPC) was updated to include the following:
  - Under '4.6 Adverse reactions' - neuromuscular troubles (uncoordinated movements, tremor) have been reported in very rare cases in *XXXXX*.
  - Under '4.10 Overdose (symptoms, emergency procedures, antidotes) – In case of accidental ingestion of the *XXXXX*, the following symptoms of poisoning may be observed: uncoordinated movements, tremor, hypersalivation. They are reversible within 24 hours. Symptomatic treatment, with benzodiazepines such as diazepam, can be initiated.
- During the time frame of the report, XXXXX received the following reports:
  - *XXXXX* suspected ADRs in animals.
  - *XXXXX* suspected ADRs in humans.
  - *XXXXX* suspected lack of efficacy.
  - *XXXXX* suspected ADRs with extra-label use.

Clinical safety

- XXXXX cases of clinical safety were reported. The majority of reports related to allergic dermal reactions locally at the neck or the complete body surface. In rare cases, very sensitive XXXXX may react more. In addition to dermal reactions, general hypersensitivity reactions were reported. It was noted that these may relate not only to deltamethrin, but also to the product's excipients. Irritation of the eyes

has been reported as a single symptom and also in combination with itching. It was thought this may also have indicated a hypersensitivity reaction.

- Generally, accidental oral intake of the XXXXX (either partially or completely) as well as extensive licking of the fur might result in signs known to occur after oral ingestion of deltamethrin. It was noted that deltamethrin has low acute toxicity to XXXXX. Further, it is rare for any reactions to been seen after intense licking of the fur. Rare cases described neurological symptoms: however, deltamethrin is released onto the coat and the fatty film covering the skin and is not absorbed systemically. The PSUR also states it is doubtful that a layperson is able to differentiate neurological symptoms due to deltamethrin from an epileptic seizure.
- Unspecified symptoms had been reported, such as anorexia, depression and lethargy. However, it was deemed difficult to assess if the deltamethrin XXXXX was the sole cause. Behaviour changes were also reported. It was deemed that these most likely occurred due to the XXXXX being unfamiliar with or disturbed by the XXXXX. Behavioural changes may also be connected to skin irritation.

Extra-label use

- XXXXX cases of extra-label use were reported. XXXXX ingesting either part or the entire XXXXX were the most commonly reported with signs associated with deltamethrin intoxication. The PSUR states that generally, deltamethrin has a high safety margin regarding acute oral toxicity XXXXX and, therefore, it was generally unlikely that oral exposure will result in a lethal intoxication. It was stated that the formulation of the XXXXX had no impact on the toxicity of deltamethrin.
- Allergic reactions were reported in two cases when the XXXXX was applied to treat flea infestation, a non-licensed indication.

Human exposure

- Fourteen cases of human exposure were reported. Effects included skin irritation, discolouration, development of acne, strange feeling of mucosal membranes, swelling of tongue and lips, fatigue, sleepiness, nausea and anxiety. It was stated that the summary of product characteristics (SPC) should include descriptions of special precautions which should be taken by the person administering the product as well as for children to avoid prolonged intensive contact with pets with the XXXXX.
- The report authors concluded that safety and efficacy of XXXXX was still in line with cumulative experience and that the risk/benefit ratio had not changed.
- The evaluator noted that the following aspects of the SPC for the European product did not appear on the proposed Australian label:
  - include descriptions of special precautions which should be taken by the person administering the product; and
  - for children to avoid prolonged intensive contact with pets wearing the *XXXXX*.

Exposure

- The evaluator indicated that the XXXXX contains XXXXX of deltamethrin. The XXXXX is intended for the protection of XXXXX. Based on the submitted data of deltamethrin the XXXXX may lose up to XXXXX of deltamethrin over the expected XXXXX lifespan of the XXXXX. The mean deltamethrin release rate would be XXXXX, assuming the XXXXX is fully charged when use commences.
- Studies showed that deltamethrin XXXXX released the active constituent onto the skin and hair of treated XXXXX. This material was then available for transfer to people interacting with the treated XXXXX.
- It was expected that exposure to the product would also occur upon application and removal of the XXXXX, primarily in a domestic setting. A semi-quantitative risk assessment of the expected exposure of homeowners, their children and workers indicated that the exposure to the active constituent through the proper use of the XXXXX would not pose an undue health risk.
- The pattern of exposure could vary depending on the level of interaction with the animal; however, it was expected to be long term daily exposure to the treated XXXXX.
- The product is currently available on the European market. Further, there were similar pesticide and insecticide XXXXX (using other active ingredients) available on the Australian market. These products were included in Schedules 5 and 6.
- The evaluator concluded that the major risk associated with the product would be a potential dermal irritation during application and normal contact with an animal wearing this XXXXX. There was also an eye irritation risk associated with use of this product which would require First Aid Instructions and Safety Directions to be established. Members noted that the safety directions included "*Do not allow children to play with* XXXXX" and considered how practical this direction might be for a family pet where the XXXXX was expected to wear the XXXXX for extended periods.

XXXXX

- The US EPA 2 per cent transfer factor probably overestimates the true dermal exposure of pet handlers, and so the above systemic dose projections were unlikely to be attained in practice.

- The evaluator concluded that no significant toxicological hazard was anticipated from exposure to deltamethrin released onto a XXXXX wearing a XXXXX through interaction with the treated animal.

XXXXX

Applicant's Response to the Evaluation Report

The Scheduling Secretariat had been advised that XXXXX had considered the evaluation report, including the scheduling recommendation of a 4 per cent cut-off instead of the requested 5 per cent cut-off, and advised that they agreed with the scheduling proposal.

October 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members 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; (c) toxicity; and (d) the dosage, formulation, packaging and presentation.

Members noted that the scheduling of deltamethrin has been extensively considered over the last 30 yr and its toxicity profile had been sufficiently established. The Committee also confirmed that, because of its high toxicity profile, the deltamethrin parent entry in Schedule 7 remained appropriate.

With regard to the delegate's query about the relevance of the adverse experiences reported in the clinical studies on workers exposed to deltamethrin, a Member reiterated the point that deltamethrin's toxicity was highly dependent on formulation and often augmented with the addition of an organic solvent. Members noted that the proposed product did not contain an organic solvent and generally agreed that this formulation would be less toxic.

A Member also indicated that the toxicity endpoints clearly suggested that deltamethrin exhibited significant interspecies variation, i.e. in general XXXXX were less susceptible than XXXXX. The Member argued, however, that this was not expected to be a major concern as very low quantities of deltamethrin would be released (approximately XXXXX of deltamethrin would be leached-out on a daily basis) and absorbed via the dermal route.

A Member noted that the product had been available on the European markets for a long time and only a few cases (14 cases) of human exposure and cutaneous paraesthesia, such as tingling, itching, burning and numbness, had so far been reported. The Member asserted that this dermal sensation was transient and reversible in nature where the affected individuals would recover in a period of hours.

A Member indicated that the risk for children; however, would be different as they could spend a considerable time with family pets. The Member stated that it was highly likely that in some cases these pets would be allowed in the bedroom accompanying children overnight. A Member was particularly concerned about cutaneous paraesthesia and asserted that it would be appropriate to require label warning statements similar to that of

the EU labels. Several Members, while noting that the labelling was a regulatory issue, asked that this issue be raised with the regulator by XXXXX. Members also recommended that the delegate additionally communicate Member's concern on this matter to APVMA.

While agreeing that the proposed presentation of deltamethrin did not require control through Schedule 7, a Member raised concern regarding inclusion of 4 per cent or less deltamethrin in Schedule 5. The Member suggested that as deltamethrin parent entry was in Schedule 7, listing 4 per cent deltamethrin in Schedule 6, rather Schedule 5, would be appropriate. Another Member noted that other aqueous preparations with a similar safety profile containing 5 per cent or less deltamethrin were already listed in Schedule 5. The Committee generally agreed that based on the toxicity profile, 4 per cent deltamethrin when impregnated in plastic resin strip materials warranted a Schedule 5 listing.

Implementation

The Committee agreed that there were no matters requiring a delayed implementation period.

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 also agreed that an implementation date of no more than six months after the final decision (i.e. 1 May 2012) was appropriate.

The delegate also decided to communicate Member's concerns, to APVMA, regarding inclusion of appropriate label warning statements on the proposed product similar to that of the EU label warning statements.

The relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits of the substance; (b) purpose and extent of use; (c) toxicity; and (d) the dosage, formulation, packaging and presentation.

DELEGATE'S INTERIM DECISION

The delegate decided to that deltamethrin, when impregnated in plastic resin strip material containing 4 per cent or less, be rescheduled from Schedule 7 to Schedule 5. The delegate decided that an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

Schedule 5 – Amendment

DELTAMETHRIN – Amend entry to read:

DELTAMETHRIN:

(a) when impregnated in plastic resin strip material containing 4 per cent or less of deltamethrin;

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

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

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

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

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

1.3 FLUXAPYROXAD

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Fluxapyroxad – seeking advice on a proposal to include fluxapyroxad in Schedule 5. Advice is also sought on whether a Schedule 6 entry may be more appropriate for fluxapyroxad.

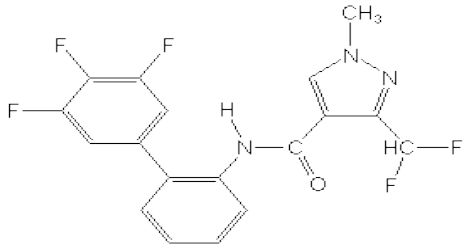
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a Schedule 5 entry be created for fluxapyroxad. The Committee also recommended an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Fluxapyroxad is a second generation carboxamide fungicide. The mode of action is inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes, and mycelial growth.

The IUPAC name of fluxapyroxad is 3-(difluoromethyl)-1-methyl-N-(3',4',5'-trifluorobiphenyl-2-yl)pyrazole-4-carboxamide. The structure is:



XXXXX submitted data to the APVMA in support of the approval of the active ingredient fluxapyroxad XXXXX. No other potential use pattern, apart from use as a fungicide, was identified.

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

SCHEDULING STATUS

Fluxapyroxad is not currently specifically scheduled. Several carboxamide fungicides are currently in Appendix B (substances considered not to require control by scheduling), including carboxin and boscalid. None of these other carboxamide fungicides appeared sufficiently similar in structure as to capture fluxapyroxad as a derivative.

INITIAL SUBMISSIONS

Applicant's submission

XXXXX Risk Assessment Technical Report found that, based on the toxicity profile (low acute oral, dermal and inhalational toxicity XXXXX and the observed slight eye irritation XXXXX) of fluxapyroxad, it would be appropriate to include this substance in Schedule 5 with no cut-off.

Other evaluator conclusions include:

- There were no objections on human health grounds to the approval of fluxapyroxad Technical Grade Active Constituent (TGAC) or XXXXX.
- The ADI for fluxapyroxad was established at XXXXX based on a NOEL of XXXXX from a two-year dietary study XXXXX and applying a default safety factor of 100 for potential inter- and intra- species variation.
- An ARfD was not established for fluxapyroxad, because no significant treatment related findings had been observed in the experimental animal database evaluated following a single dose administration of fluxapyroxad, which would be likely to present an acute hazard to humans.

XXXXX

Members noted that an international toxicology assessment of fluxapyroxad was conducted jointly by scientists from XXXXX Since the XXXXX report relied significantly on international assessment collaboration, a LOAEL and NOAEL rather than a LOEL and NOEL approach was used based on the scientific justification for their adoption in the international assessment report.

Toxicology

Members noted the following toxicology summary for the TGAC fluxapyroxad.

- XXXXX

- Fluxapyroxad had low acute oral dermal and inhalational toxicity XXXXX. It was a slight skin irritant but not an eye irritant XXXXX or not a skin sensitiser XXXXX.

- Skin irritation: In a skin irritation study XXXXX were exposed to a single dermal application of XXXXX. No oedema was observed during the study. Slight erythema was observed in XXXXX exposed animals immediately after removal of the patch and persisted XXXXX for up to XXXXX. All dermal irritation was resolved by XXXXX. The evaluator concluded that fluxapyroxad was a slight skin irritant to XXXXX and recommended a Schedule 5 listing without cut-off.

- Fluxapyroxad is not considered to be *in vivo* genotoxic or *in vitro* non mutagenic or genotoxic.

- The evaluator indicated that the developmental toxicity effects in offspring in response to fluxapyroxad were limited to decreased XXXXX body weights and body weight development XXXXX at maternotoxic dose levels. The evaluator asserted that fluxapyroxad was not a developmental toxicant XXXXX.

Specific issues flagged by the delegate – carcinogenic effects

The Committee noted the delegate's concern on the carcinogenic effects (especially adenomas and carcinomas) of the substance and considered the proposed mode of action (MOA) of fluxapyroxad and the significance of these findings. The following summarises the evaluator's findings on this matter:

- In a long-term carcinogenicity study, dietary doses of XXXXX were administered to XXXXX. Hepatocellular tumours in the form of adenomas and carcinomas were observed in XXXXX, with a significant increase in the combined incidence of these tumour types XXXXX. Significant increases in hepatocellular carcinomas were observed only XXXXX. Adenomas were observed XXXXX at a higher incidence than carcinomas and at lower doses. Significant increases in adenomas were observed XXXXX The evaluator, however, noted that adenoma incidence was

greater than the upper limit of historical controls XXXXX at and above XXXXX, and so was determined to be an effect of treatment.

- Non-neoplastic changes in the livers of these animals included increases in the absolute and relative liver XXXXX in conjunction with centrilobular hepatocellular hypertrophy, spongiosis hepatis XXXXX, increased pigment storage (likely lipofuscin) XXXXX, and dark brown liver discoloration XXXXX.
- The evaluator indicated that human relevance of liver tumours XXXXX via the proposed MOA was equivocal. The proposed MOA for liver tumours was that fluxapyroxad works through a mitogenic MOA, whereby cell proliferation in the liver progresses to adenomas and carcinomas. This occurs in the context of other changes in the liver that are commonly associated with these effects (e.g. enzyme induction, hepatocellular hypertrophy, increased liver weights, enlarged liver, and non-neoplastic alterations in the liver at the gross and microscopic level).
- The evaluator further indicated that phenobarbital was used as a positive control in some of the thyroid mechanistic studies (e.g. ^{125}I uptake and perchlorate discharge). These thyroid effects were influenced by liver enzyme regulation, and the results were similar to fluxapyroxad. Phenobarbital was also known to work via a mitogenic MOA with key events similar to the ones proposed for fluxapyroxad. The relevance of tumours that occur via this MOA to humans was equivocal, however, no clear relationship between phenobarbital exposure and hepatotumourgenesis had been established. Therefore, use of this (similar) MOA for fluxapyroxad was considered conservative, as it was not clear that liver tumours that occur via this MOA would be observed in humans.
- The evaluator asserted that mechanistic studies demonstrated that a non-genotoxic mitogenic mode of action for liver tumour formation was operative XXXXX, whereby fluxapyroxad causes increased cell proliferation leading to adenoma formation with a clear threshold for these effects. Furthermore, key events in the fluxapyroxad liver tumour formation were similar to those for phenobarbital for which no clear relationship between phenobarbital exposure and hepatotumourgenesis was observed in humans. Consequently, taking a conservative approach the relevance of these tumours to humans was equivocal at best. The evaluator concluded that the observed liver tumours XXXXX were of limited relevance to humans.

Specific issue flagged by the delegate – discoloured teeth.

The Committee considered the delegate's request for advice on discoloured teeth. Several fluxapyroxad toxicity studies resulted in discoloured teeth in treated animals and this was considered to be unusual. The following summarises the evaluator's findings on this matter:

- In a two-generation reproduction toxicity study, fluxapyroxad was administered in the diet to groups of XXXXX throughout 2 generations. No treatment-related mortality was observed during the study in parental animals or offspring. Treatment-related clinical observations were restricted to a whitening of maxillar or mandibular incisors

at the high dose. In addition to this, changes in bone thickness also observed. The evaluator asserted that these effects were not considered adverse. The evaluator noted that these non adverse finding in teeth and in long bones (not skull bones) may be related to changes in iron storage in these tissues. A limited histopathological examination of teeth indicated that the discoloration/whitening of teeth probably was due to a reduced incorporation of an iron containing pigment into the outer enamel. Teeth discoloration did not affect the normal histomorphology of the teeth and this was also demonstrated in satellite group animals of the chronic XXXXX studies. The evaluator concluded that this treatment-related effect was not considered to be adverse.

- In a carcinogenicity and long-term toxicity study, animals were treated with fluxapyroxad XXXXX to assess carcinogenicity. A satellite group of animals was sacrificed at one year to assess chronic toxicity. Treatment-related clinical observations were restricted to a white discoloration of the teeth XXXXX as well as a dark brown discoloration of the liver XXXXX. All other macroscopic findings were observed in single cases only, displayed no dose-response relationship or were equally distributed between control and treated groups. The histopathological examination of the teeth did not reveal differences between control and treated groups. Thus it was decided not to perform histopathological investigations of the teeth of the main (carcinogenicity) group animals. Further investigation of teeth whitening was performed in single animals of XXXXX. The evaluator noted that the whitening of teeth was most likely due to a decreased deposition of a yellow iron containing pigment in the "outer enamel" layer of the teeth. The evaluator asserted that this finding was considered to be non-adverse since no other morphological alterations in tooth structures could be detected, which might give indications for the pathology underpinning the clinical and macroscopic finding of "teeth whitening" (e.g. fluorosis).

Specific issue flagged by the delegate – neuropharmacological effects.

The Committee considered the delegate's concern regarding the neuropharmacological effects on treated animals following bolus dosing:

- In an acute neurotoxicity study, groups of XXXXX were administered XXXXX of fluxapyroxad. No signs of general systemic toxicity were observed. Treatment-related neurobehavioral effects were noted in mid and high dose animals only on the day of treatment. These consisted of slight, but statistically significant increase of the landing foot-splay in high dose XXXXX, reduction in the number of rearings XXXXX as well as impaired motor activity in high and mid dose XXXXX and XXXXX. No effects on these parameters were observed on study days XXXXX. Additionally, no treatment-related neuropathological findings were noted, i.e. no brain weight changes or neurohistopathological findings were observed. The evaluator asserted that the affected clinical parameters were considered to be an indication of a neuropharmacological effect rather than an indication of neuronal damage. The LOAEL is XXXXX, based on decreased motor activity XXXXX and decreased rearing XXXXX. The NOAEL was XXXXX. The evaluator indicated that

although decreased rearing XXXXX and decreased motor activity were observed XXXXX, there was no evidence of histopathological effects or alterations in brain weights.

- In a 90 day neurotoxicity study groups of XXXXX were administered dietary levels XXXXX. This did not result in any clinical (general clinical observation, FOB and motor activity) or neurohistopathological indication of neurotoxicity. Signs of systemic toxicity observed in this study such as slightly impaired body weight development in high-dose XXXXX, changes of clinical chemistry parameters (increased serum g-GT, total protein, albumin, globulin, cholesterol, triglycerides, urea, Ca^{2+}, inorganic PO_4^- and Mg^{2+} levels as well as decreased AS(A)T, glucose and bilirubin levels), increased liver and thyroid weights as well as centrilobular hypertrophy of hepatocytes. The evaluator indicated that under the conditions of the study, the NOAEL for neurotoxicity was XXXXX, the highest dose tested, which was equivalent to about XXXXX. The NOAEL for neurotoxicity was XXXXX. A LOAEL was not observed.
- The evaluator asserted that these effects were observed on the day of dosing only and no evidence of neurotoxicity was observed in the short-term dietary neurotoxicity study or elsewhere in the toxicity database. The evaluator concluded that the observed transient clinical effects of fluxapyroxad were an indication of a neuropharmacology effect rather than an indication of neuronal damage.

Hazard classification

- The evaluator advised that fluxapyroxad was not listed on Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2011).

Product XXXXX

- Members noted the acute toxicity profile of the product containing XXXXX of fluxapyroxad.

XXXXX

- The product had low acute oral, dermal and inhalational toxicity XXXXX. It was a slight skin, but a severe eye irritant XXXXX. It was not a skin sensitiser XXXXX.
- Eye irritation: an eye irritation study conducted XXXXX with a concentration of XXXXX of fluxapyroxad resulted in slight corneal opacity, moderate iritis, slight to severe conjunctival redness, slight to marked conjunctival chemosis and slight to severe discharge. Additional findings like contracted pupil, discharge of blood, circular vascularisation of the cornea into the central part or marginal as well as circular injected scleral vessels were also noted. The ocular reactions were not reversible in the animal within study termination (XXXXX after application). Slight

corneal opacity (more than 75 per cent of the area), contracted pupil, circular vascularisation into the central part of the cornea and circular injected scleral vessels were still observed in the animal at study termination. The evaluator, based on the cornea opacity and circular injected scleral vessels at XXXXX, concluded that the product was a severe eye irritant.

Exposure

- The product was a new fungicide and would be used XXXXX. However, professional and contract workers usually travel from farms to farms to carry out spraying operations and, thus, could potentially be exposed to fluxapyroxad all year round. The most likely route of exposure to the product would be dermal and inhalational, and the duration of exposure was expected to be chronic (to protect professional/contract workers).
- Farmers and their employees would be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills, maintaining equipment and entering treated areas. The main route of exposure to the product would be dermal and via inhalation, although ocular exposure is also possible.
- There would be several possible post application activities that may be required to be carried out in treated fields. These include the low exposure activities such as scouting, weeding and thinning of immature plants.
- There were no proposed home garden uses for this product. Based on the acute toxicity hazard profile of both the active constituent fluxapyroxad and the product and the proposed use of the product, there was not expected to be any risk to the public from accidental exposure from overspray/spraydrift.
- The evaluator indicated that since the NOEL was derived from an animal toxicity study, a margin of exposure (MOE) of 100 or above would be considered to be acceptable. The MOE takes into account both interspecies extrapolation and intraspecies variability.
- XXXXX
- The evaluator noted that estimated MOEs were acceptable (i.e. >100) during application activities when using XXXXX whether the operator wears gloves or not. However, during mixing and loading, for each use scenario the MOEs were unacceptable without gloves, therefore the use of gloves to mitigate dermal exposure was required to reduce exposure to an acceptable level.

XXXXX

Applicant's Response to the Evaluation Report

The evaluator advised that XXXXX had considered the evaluation report, including the scheduling recommendation, and advised that they agreed with the evaluator's scheduling proposal.

October 2011 Pre-meeting Submissions

Two pre-meeting submissions XXXXX were received.

XXXXX supported the evaluator's recommendation i.e. inclusion of fluxapyroxad in Schedule 5 with no cut-off.

XXXXX did not state a position with regard to the delegate's scheduling proposal, but did provide a number of specific comments against section 52E:

Risks and benefits

- Noted that the substance could be used against disease resistant management. When a chemical was used repeatedly, pathogens can quickly develop resistant against the chemical. Asserted that disease resistant could be delayed by mixing fluxapyroxad with other existing chemicals (two modes of acting chemicals in a combined spray). The submission argued that this would increase the longevity of several other chemicals and would be a valuable tool in disease management.

Extent and pattern of use

- Reiterated that as the substance had the ability to control three to four species of disease causing fungi, it had a broad fit in horticulture, such as vegetables, grapevines and topfruit. Also noted that fluxapyroxad for used as a cereal fungicide was being developed in other countries.

Purpose

- Noted that this substance was a new generation carboxamide fungicide and several companies were developing similar carboxamide fungicides. Argued that as carboxamide were solely used as a fungicide, it could also be considered in agronomic fungal disease control similar to that of boscalid (which was the original carboxamide fungicide).

EXPERT ADVISORY COMMITTEE DISCUSSION

Members noted that the relevant matters under section 52E (1) of the Therapeutic Goods Act 1989 included (a) risks and benefits; and (c) toxicity.

The Committee noted that fluxapyroxad had a low acute toxicity profile consistent with the Schedule 5 factors. Members also noted that, for the product XXXXX, the severe eye

irritation observed XXXXX, met the factor for Schedule 6 listing. However, this acute toxicity appears to arise from the product formulation, e.g. solvents / excipients, rather than the toxicity of the active constituent fluxapyroxad. A Member asserted that these formulation-related irritation effects are not a driver of scheduling. Members generally agreed that such toxicity was an issue for the regulator as part of any product approval process, separate to scheduling.

The Members then discussed whether fluxapyroxad-induced carcinogenicity, teeth discolouration and neuropharmacological effects, as raised by the delegate, were sufficiently concerning as to warrant more restrictive scheduling.

Carcinogenicity

- A Member indicated that fluxapyroxad liver toxicity varied among different species of animals and this was prominently shown XXXXX. A Member noted that the evaluation report, supported with robust data, indicated that the proposed MOA for liver tumours was through a mitogenic MOA, whereby cell proliferation in the liver progressed to adenomas and carcinomas. This occurred in the context of other changes in the liver that are commonly associated with these effects. Several Members asserted that relevance of liver tumours XXXXX via the proposed MOA was equivocal with limited generalisability and unlikely to occur in humans. A Member indicated that this would probably be a risk communication issue rather than a scheduling issue.

Teeth discolouration

- A Member noted that there was limited information regarding teeth discolouration in the evaluation report. The Member speculated that the discolouration of teeth may be due to fluorosis from fluoride ions released as a consequence of fluxapyroxad metabolism. The Member asserted that discolouration of teeth was limited to enamel and did not have histological effects. The Member further noted that as XXXXX, so the opportunity for absorption of fluxapyroxad and teeth whitening was highly likely. The Member, however, argued that as this was not the case for adult human teeth, this effect was incidental and not relevant to humans.

Neuropharmacology

- A Member noted that neuropharmacological effects resulted in decreased motor activity and asserted that as this was reversible, therefore the effect was minor. The Member also asserted that these neuropharmacological effects did not result in neuronal damage. Another Member, however, argued that whether reversible or not, the pesticide's neuropharmacology effects were of concern and required risk management. The Member indicated that neuropharmacological effects may impair a person's ability to operate machinery and which could be sufficiently serious to warrant a Schedule 6 listing for fluxapyroxad. Other Members, however, disagreed.

As a separate matter, a Member noted that fluxapyroxad persists in the environment for a long time. The Committee was, however, informed that as it did not have bioaccumulation properties this was not a human toxicity issue. Another Member noted that such environmental matters would be considered by the agency responsible for environment. The Committee generally agreed that, based on its toxicology profile, a Schedule 5 listing for fluxapyroxad was appropriate.

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 also agreed that an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012) was appropriate.

The relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits of the substance and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate decided that a Schedule 5 entry be created for fluxapyroxad. The delegate also decided an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

Schedule 5 – New entry

FLUXAPYROXAD.

1.4 INDAZIFLAM

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Indaziflam – seeking advice on a proposal to include indaziflam in Schedule 6.

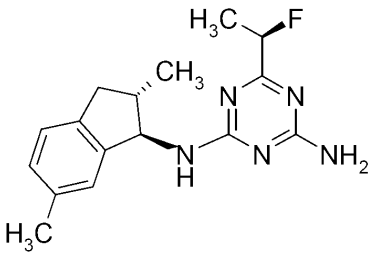
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a Schedule 6 entry be created for indaziflam. The Committee also recommended an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Indaziflam is a fluroalkyltriazine that inhibits cellulose biosynthesis and therefore inhibits seed growth prior to germination and during root development. Indaziflam requires activation by rainfall or irrigation within weeks of application.

The IUPAC name for indaziflam is N-[(1R,2S)-2,6-dimethyl-2,3-dihydro-1H-inden-1-yl]-6-[1RS-1-fluoroethyl]-1,3,5-trazine-2,4-diamine and the structure is:



XXXXX submitted data to the APVMA seeking the approval of the active ingredient indaziflam and the registration of a XXXXX No other potential use pattern, apart from use as a herbicide, was identified.

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

SCHEDULING STATUS

Indaziflam is not currently specifically scheduled and there is no current entry that would capture indaziflam as a derivative, nor any group entry that would capture this chemical.

SUBMISSIONS

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission recommended a Schedule 6 entry for indaziflam, based on the toxicity profile (mainly because of its neurotoxicity potential). The evaluator also indicated that a cut-off from Schedule 6 for indaziflam was not warranted due to the steepness of the dose response curve for neurotoxicity and that no neurotoxicity studies on the product were available.

Other evaluator conclusions included:

- There were no objections on human health grounds to the approval of indaziflam Technical Grade Active Constituent (TGAC) XXXXX.
- No ADI or ARfD was established for indaziflam because it was not intended for use in food producing agriculture.

Toxicology

Members noted the following toxicology summary for the TGAC indaziflam:

XXXXX

- Indaziflam had low acute oral XXXXX and dermal XXXXX toxicity XXXXX. It was not a skin irritant, but was a slight eye irritant XXXXX. It was not a skin sensitiser XXXXX.
- Inhalational toxicity: Indaziflam's inhalational LC_{50} value was XXXXX Members noted that the LC_{50} value aligns with the Scheduling Policy Framework's (SPF) Schedule 6 factor for this endpoint. An inhalational toxicity study conducted in XXXXX resulted in mydriasis, piloerection, ungroomed hair coat, red tears, bradypnea, laboured and irregular breathing, reduced motility, limp, tremor, high legged and staggering gait, clonic salutatory spasm and vomiting. All treated animals presented with mydriasis upon light reflex testing, while XXXXX presented with reduced corneal reflex. XXXXX animal responded with an abnormal and aggressive startle reflex. No clinical signs were noted after XXXXX. No abnormalities were found during necropsy. Rectal temperatures were measured approximately half an hour after the exposure period and the tested groups showed a decreased temperature compared to the controls.
- There was no evidence of carcinogenic potential in long-term XXXXX studies.
- Indaziflam in *in vitro* and *in vivo* mutagenicity and genotoxicity studies showed negative effects. *In vitro* mutagenicity and genotoxicity studies on the metabolite indaziflam-carboxylic acid and 6-(1-fluorophenyl)-1,3,5-triazin-2,4-diamine were also negative.
- No reproductive or developmental toxicity was observed at doses that were not maternotoxic. Reproductive toxicity (decreased number of implants, corpora lutea and litter size) was observed at maternotoxic doses and was considered a secondary non-specific consequence of such.

Specific issue flagged by the delegate – Neurotoxicity.

- Neurotoxicity was of concern as the nervous system was the target organ for indaziflam's toxicity. The Members noted the delegate's comment on the adverse effects of neurotoxicity findings XXXXX and to a lesser extent XXXXX and considered whether a Schedule 6 entry for indaziflam was appropriate based on these effects. Members noted that the evaluator's recommended Schedule 6 entry appears largely based on the neurotoxicity findings, noting this also appears to be supported by the inhalational LC_{50}. Members considered the delegate's request for advice on whether the neurotoxicity may be a class effect (whether the mode of action of indaziflam could be identified). Members, however, noted that the evaluation report had limited information on class effects or the specific mode of action of indaziflam.
- The neurotoxicity findings XXXXX ranged from axonal degeneration XXXXX respectively in a chronic study to neuromuscular seizures leading to sacrifice *in extremis* XXXXX in a subchronic study with dosing at this level, which ceased on XXXXX. Indaziflam exhibited neurotoxicity potential XXXXX at varying dose levels.

- In a 90-d neurotoxicity study, XXXXX were administered with indaziflam XXXXX by oral gavage. Severe clinical signs of toxicity were noted XXXXX. Neuromuscular seizures were observed in all three affected animals. XXXXX also exhibited tremors, ataxia, laboured breathing, no reaction to light and decreased activity. The seizures were noted XXXXX on day 15 and XXXXX on days 22 and 35 respectively, and animals were sacrificed *in-extremis* on these days. All other XXXXX were sacrificed on the basis of these clinical signs on day 36. Therefore, all results from the XXXXX were not a result of dosing for 90 d. No mortalities were observed XXXXX, and clinical examination did not reveal overt treatment related signs of toxicity, with the possible exception of salivation in XXXXX, which occurred at the same incidence as in the XXXXX.
- Several effects were observed in the central nervous system XXXXX. Axonal degeneration was noted in the brain, spinal cord and the sciatic nerve. This effect was most notable in the sensory tract of the spinal cord and sciatic nerve XXXXX and the incidence and severity suggested a dose response XXXXX. Axonal degeneration was only observed in the brain XXXXX. There were borderline effects at XXXXX that were not seen in control animals, such as axonal swelling, lymphocytic inflammation and nerve fibre degeneration. Although the incidence and severity of these effects were low, the incidence of axonal swelling increased from XXXXX. Although the incidence decreased or was not observed at the top dose of XXXXX the evaluator considered that as these animals were sacrificed early due to signs of overt toxicity asserting that these effects could not be entirely dismissed. Therefore, the evaluator concluded that the axonal swelling in the sensory tract of the spinal code XXXXX and axonal swelling in the brain XXXXX were treatment related.
- The evaluator noted that data for neurotoxicity showed considerable species differences XXXXX. A battery of neurotoxicity studies XXXXX (acute, subchronic and developmental) confirmed the neurotoxic potential of indaziflam at higher doses XXXXX based on decreases in motor and locomotor activity and axonal degeneration, but did not demonstrate delayed or developmental neurotoxicity. The chronic and subchronic XXXXX studies show clear histopathological changes. For example, in a 90-day study, XXXXX were administered 0, 7.5, 15 or 30 mg/kg bw/d by oral gavage. The XXXXX groups were sacrificed approximately one month into the study and are considered mortalities as a result. This highlights a clear toxic dose at XXXXX due to neuromuscular seizures and other related neurological effects (ataxia, tremors) observed in both sexes. Changes observed in the blood, urine and organ weights were sporadic and not considered to be treatment related. Treatment related microscopic findings (cysts) were observed in the ovaries of females at XXXXX. Additionally, treatment related findings were seen in the central nervous system of XXXXX in all treatment groups. The effects seen at the XXXXX (axonal swelling, lymphocytic inflammation and nerve fibre degeneration) were not observed in controls and although of low incidence and severity the findings of axonal swelling were considered likely to be treatment related adverse effects, as a dose response was observed at XXXXX. The evaluator asserted that it cannot be entirely dismissed that

the decrease or absence of these finding at XXXXX was due to the early sacrifice of all animals at this dose.

Hazard classification

· Indaziflam was not listed on Safe Work Australia's (SWA) Hazardous Materials Information System (HSIS) Database (SWA, 2011). With the available toxicology information, the evaluator concluded that indaziflam should be classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases; when present at 10 per cent or more:

Xn: R48/22	Harmful: Danger of serious damage to health by prolonged oral exposure

Formulated Product – XXXXX *indaziflam).*

· Members noted the following toxicology data for the XXXXX indaziflam product.

Toxicity end point	Toxicity of product
Oral	Low toxicity
Dermal	Low toxicity
Inhalational	Low toxicity
Skin irritation	Non-irritant
Skin corrosion (*in vitro*)	Non-corrosive
Eye irritation	Slight irritant
Skin sensitisation	Non-sensitiser

· The product had low acute oral XXXXX dermal XXXXX and inhalational XXXXX toxicity XXXXX. It was not a skin irritant XXXXX and was non-corrosive *in vitro* to reconstructed human epidermis. It was a slight eye irritant XXXXX and was not a skin sensitiser XXXXX.

· The evaluation report noted that the available data indicates the nervous system was a target organ for indaziflam toxicity. The active ingredient's neurotoxicity studies indicate that there was a big difference in sensitivity between XXXXX, based on the neurotoxic findings XXXXX ranging from axonal degeneration XXXXX respectively in a chronic study to neuromuscular seizures leading to sacrifice *in extremis* in XXXXX in a subchronic study (dosing at this level ceased on day 36), therefore a Schedule 6 was appropriate for indaziflam. The steepness of the dose response curve for neurotoxicity and that there were no studies on the product which contains XXXXX, did not sufficiently establish the product would be a low to moderate hazard and thus supported a cut-off.

Exposure

- XXXXX As the product may be applied XXXXX therefore re-entry exposure was possible for members of the public. Of particular concern were children that may have direct dermal contact, leading to hand to mouth contact with the product. These exposure risks were unlikely to be of concern as the margin of exposure (MOE) for workers and public entering treated areas was acceptable on day zero.
- Based on the toxicity hazard profile of both the active constituent and the product and its proposed use pattern, there was not expected to be any risk to the public from accidental exposure to the product from overspray/spraydrift.
- Farmers and their employees would be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application and cleaning up spills and equipment. The main routes of exposure to the product/spray will be dermal and inhalation, although ocular exposure would also be possible.

XXXXX

- The evaluator noted that the MOEs for XXXXX were all acceptable (>100) when the operator was wearing a single layer of cotton overalls, with and without gloves. Therefore, these application methods were not expected to pose an undue hazard to human health when the operator was wearing a single later of cotton overalls.
- The MOE for XXXXX was acceptable (>100) only when the operator was wearing gloves and a 2nd layer of clothing during application.
- The MOE for workers and the public entering treated areas was acceptable on day zero XXXXX. Therefore, there was no re-entry risk associated with Specticle Herbicide after the spray has dried. The evaluator noted that the following re-entry statement was recommended for the product label: "*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*."

XXXXX

Applicant's Response to the Evaluation Report

The applicant had seen a copy of the evaluation report and has informed the evaluator that they had no comments.

October 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (c) toxicity.

The Committee noted that although indaziflam's low acute toxicity end-points and low accumulation potential may align with a Schedule 5 listing, neurotoxicity potential was a concern and a Member indicated that appropriate scheduling controls should be in place to mitigate this risk. Some Members were also concerned that these MOE values may not be applicable to agricultural use of indaziflam if used in the production of food crops in future, since the low MOE were generated using a non food producing model. It was noted that indaziflam is used on food crops in some overseas countries. Several Members also noted that interspecies variation in the neurotoxicity findings, together with the steepness of the dose response curve for these findings, raised questions regarding the relevance to humans.

A Member additionally asserted that the limited information in the evaluation report and available literature on indaziflam's neurotoxicity effects were insufficient for the Committee to make an informed recommendation on allowing down scheduling to Schedule 5. The Member also noted that indaziflam contains a triazine moiety within its chemical structure, therefore was likely to disrupt the hypothalamic-pituitary-gonadial axis. The Member, however, indicated that the US Environmental Protection Authority (EPA) (a full report is available at www.epa.gov/opprd001/factsheets/indaziflam.pdf) had excluded indaziflam from the triazine group. The Committee generally agreed that a Schedule 6 listing was appropriate for indaziflam.

Based on the product's low acute toxicity profile, Members considered a low concentration cut-off to Schedule 5 for preparations containing 20 per cent or less of indaziflam. A Member also noted that the applicant had not provided neurotoxicity studies on the product. Members agreed that such a low concentration cut-off may not be appropriate at this time due to lack of neurotoxicity data and interspecies variation.

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 also agreed that an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012) was appropriate.

The relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits of the substance; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The decided that a Schedule 6 entry be created for indaziflam. The delegate also decided an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

Schedule 6 – New entry

INDAZIFLAM.

1.5 PROSULFURON

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Prosulfuron – seeking advice on a proposal to include prosulfuron in Schedule 6 with a possible cut-off to Schedule 5 for preparations containing 5 per cent or less of prosulfuron.

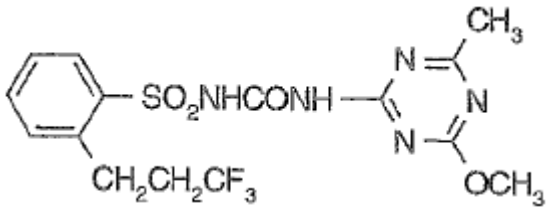
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 6 entry be created for prosulfuron. The Committee further recommended that a lower concentration cut-off to Schedule 5 listing at 5 per cent or less of prosulfuron was not appropriate. The Committee also recommended an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Prosulfuron is a member of the sulfonylurea class of pesticides. It inhibits the branched-chain amino acid biosynthesis, and consequently depresses cell division at the root tips. Growth of susceptible plant species is rapidly inhibited via acetolactate synthase inhibition, with plant death occurring in 14 to 21 d post-application.

The IUPAC name for prosulfuron is 1-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-3-[2-(3,3,3-trifluoropropyl)phenylsulfonyl]urea and the structure is:



XXXXX had submitted data to the APVMA seeking approval of the active ingredient prosulfuron and XXXXX. No other potential use pattern, apart from use as a herbicide, has been identified.

XXXXX.

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

SCHEDULING STATUS

Prosulfuron is not currently specifically scheduled. Several other sulfonylurea pesticides are listed either in Appendix B (including bensulfuron-methyl and metsulfuronmethyl) or Schedule 5 (including sulfometuron-methyl, chlorsulfuron and thifensulfuron). Prosulfuron may have a sufficiently similar structure to some of these other sulfonylurea pesticides that it may be captured as a derivative of one of these substances.

INITIAL SUBMISSIONS

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission recommended, based on the toxicity profile of prosulfuron (moderate to high acute oral toxicity, low dermal and inhalational toxicity XXXXX, not a skin irritant or skin sensitiser XXXXX but was a slight eye irritant XXXXX) a Schedule 6 listing with a cut-off of 5 per cent or less to Schedule 5 for prosulfuron.

Other XXXXX recommendations include:

- There were no objections on human health grounds to the approval of prosulfuron TGAC or XXXXX.
- No ADI or ARfD for prosulfuron was currently required, since the proposed product use pattern was not for food producing use.

Toxicology

Members noted the following toxicity data for technical grade active constituent (TGAC) prosulfuron:

XXXXX

- Prosulfuron had moderate to high acute oral toxicity XXXXX, low dermal XXXXX and inhalational XXXXX acute toxicity, and was not a skin irritant or sensitizer XXXXX. It was a slight eye irritant XXXXX.
- Oral toxicity: XXXXX was administered to XXXXX per dose level, and XXXXX to XXXXX. Clinical signs of toxicity were seen XXXXX. The symptoms included: hypoactivity, staggered gait, red-stained faeces and soft stool. Additionally, dark-
- stained urogenital area and lacrimation were seen XXXXX along with hypersensitivity to sound at XXXXX hypersensitivity to touch and dyspnoea were observed at XXXXX There was, however, no significant effect on body weight gain

in animals surviving to termination. Based on the test conditions, the oral LD_{50} XXXXX for prosulfuron was XXXXX

- In another acute oral toxicity study, XXXXX groups XXXXX were administered with prosulfuron as a single oral gavage dose at XXXXX animals treated at XXXXX, and XXXXX animal (sex not reported) treated at XXXXX, died within XXXXX of test material administration. Clinical signs of toxicity XXXXX included hypoactivity and staggered gait at XXXXX, and hypersensitivity to sound at XXXXX. There was no significant effect on body weight gain in animals surviving to study termination. Test material related macroscopic findings were limited to the presence of white tenacious semisolid material in the duodenum and/or jejunum in XXXXX animals treated at XXXXX which died during the test. No macroscopic findings were seen in animals surviving to study termination. Based on the test conditions, the oral LD_{50} in XXXXX.
- Carcinogenicity: Members noted that the delegate had requested the Committee's advice on the findings of testicular interstitial cell and thyroid tumours in males and mammary gland adenocarcinomas, adenomas and fibromas in females.
- XXXXX dietary study an increase incidence of testicular interstitial cell tumours was seen at XXXXX. The incidence was only (slightly) outside the historical control range at 2000 ppm but not at the top dose, 4000 ppm. The study found that at 2000 ppm the survival rate XXXXX was nearly double that of the control XXXXX Tumours of the testes tend to occur in older animals, so the enhanced survival, particularly in the 2000 ppm group, would increase the chance that an animal would develop a tumour in the testes. Furthermore, as there was a slight difference in survival between the control and 2000 ppm group, statistical analysis of the incidence of tumours was undertaken adjusting for survival rates. No statistically significant increase was seen in any tumour type. The evaluator asserted that not only was there no dose response but there was no progression to malignancy or supportive treatment related non-neoplastic changes in the testes that would suggest that the observed tumours occurred by a chemical carcinogenesis mechanism.
- The evaluator concluded that the non-significant statistical finding of an increased incidence in benign testes tumours compared with controls, (slightly outside the historical control range at XXXXX but not XXXXX and seen in the absence of associated treatment related non-neoplastic histopathological changes to the testes), was likely to be incidental and not treatment related.
- The evaluator further noted that in females, increased incidence of mammary gland adenocarcinoma, adenoma and fibroma were seen. Correction for the slightly better survival in XXXXX females XXXXX compared to controls XXXXX showed no statistical significance in mammary gland tumour findings. A statistical analysis of the mammary tumour onset time distribution did not demonstrate a statistically significant effect of treatment. The evaluator noted that not only was there no dose response for the observed tumour findings, but there was no consistency for each tumour in the dose producing the greatest incidence (XXXXX for fibromas and XXXXX for adenocarcinomas and adenomas). Furthermore, there was no supportive

treatment related non-neoplastic changes in the mammary gland in females that would suggest the observed tumours occurred by a chemical carcinogenesis mechanism.

- The evaluator concluded that increased incidence of mammary gland tumours findings was not statistically significant compared to concurrent controls or dose related, and were seen in the absence of associated treatment related non-neoplastic histopathological changes to the mammary gland, were likely to be incidental and not treatment related.
- Neurotoxicity: The evaluator indicated that evidence of transient neurotoxicity was observed in an oral (gavage) acute neurotoxicity study XXXXX, with the most affected functional observational battery parameters being neuromuscular functions (ataxic and/or abnormal gait, impaired righting reflex) and rectal temperature at the time of peak effect XXXXX. Similarly, figure-8 maze activity counts were also affected at the time of peak effect only XXXXX as the mean of the total sessions or by time interval. No such findings were seen in a XXXXX dietary study XXXXX at similar dose levels. The evaluator asserted that the method of administration, (gavage in the acute neurotoxicity versus dietary in this study), was a likely factor in the difference in findings between the two studies, which consisted of transient neurotoxicity findings in the acute study and concluded that prosulfuron was not considered to be a neurotoxic hazard to humans.
- Developmental toxicity: The evaluator noted that in all the oral (gavage) developmental studies XXXXX a consistent finding was an increase in the incidence of minor skeletal variations in the presence of marked maternal toxicity (decreased body weight gain). The evaluator concluded that prosulfuron was not considered to be a developmental toxicant XXXXX as the observed skeletal findings were seen in the presence of marked maternal toxicity and considered a secondary non-specific consequence of such.
- Prosulfuron was not considered to be an *in vivo* genotoxicant or to be mutagenic or genotoxic *in vitro*.
- Prosulfuron was not a reproductive toxicant in a two-generation reproduction study XXXXX

Hazard classification

Prosulfuron is listed on the Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2011) with the following risk phrase (with a cut-off of less than 25 per cent):

Xn; R22	Harmful if swallowed

With the available toxicology information, the evaluator considered that the current classification of prosulfuron on HSIS according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) was appropriate.

*Product X*XXXXX

Members noted the toxicity profile of the product:

XXXXX

- The product containing XXXXX was of low acute oral and dermal toxicity, a slight eye and skin irritant XXXXX and neither a skin irritant XXXXX nor a skin sensitizer XXXXX. Members noted that the evaluator indicated that the acute toxicity end-points were based on a test formulation, rather than the proposed product formulation. The difference between the test formulation and the proposed product was minor, where formulation changes included XXXXX. The evaluator asserted that studies with the test formulation were considered acceptable for the purpose of this assessment in determining the acute toxicity profile of the proposed product.
- Eye irritation: in an eye irritation study, XXXXX of the test material was applied into the conjunctival sac XXXXX. Apart from corneal opacity observations, discharge was only seen in the animals receiving local anaesthetic and these animals had a slightly higher conjunctival erythema at XXXXX. At XXXXX and XXXXX, the degree of conjunctival erythema was the same in all animals, as was its persistence (i.e. conjunctival erythema was reversible in all animals at XXXXX).
- The evaluator asserted that since corneal opacity was only seen in XXXXX animal (that received anaesthetic) and not from XXXXX onwards, it was not considered sufficient evidence to demonstrate a moderate eye irritation potential. The evaluator further noted that this was supported by the severity of the only other effect seen, minimal to moderate conjunctival erythema which was reversible in all animals by XXXXX. The evaluator concluded that the product exhibited a slight not a moderate eye irritation potential in this study.

Exposure

- The product was proposed to be used as XXXXX. The product should be applied XXXXX per season, or a repeat application after XXXXX weeks if lower rates were used in high weed pressure situations, or during extended germination periods due to environmental conditions.
- XXXXX, maintenance workers and professional pesticides contractors would be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application, cleaning up spills, maintaining equipment and entering treated areas. The main route of exposure to the product during dilution and spray will be dermal, though inhalation and ocular exposure were also likely. The main issue with the product was slight eye irritancy and this issue could be managed by the use of personal protective equipment.
- Based on the product use pattern, the use period would extend to no more than XXXXX weeks, and worker exposure was likely to be short term repeat use of the product during this period.

- The product was not intended for domestic use and would not be used in food-producing crops. Based on the hazard profile of both the active constituents and the product and the proposed use of the product as a diluted spray, the risks to the public from accidental exposure to the product from bystander overspray/spray-drift were expected to be low.
- The product may be used in publically accessible areas and the main route of public exposure would be via re-entry to treated areas. Although post-application exposure may involve high exposure-equivalent activities involving direct contact with treated turf while playing sport, such exposure was likely to be infrequent and limited in extent, and hence the risks were expected to be low. The evaluator recommended a re-entry statement indicating "*Do not allow the general public to enter treated area until the spray has dried*".
- Margin of Exposure (MOE) estimates for workers using the product XXXXX included:

XXXXX

- The evaluator indicated that the MOE for ground-boom application was acceptable for prosulfuron when the operator was wearing a single layer of PPE with or without gloves. Therefore, this application method was not expected to pose an undue hazard to human health when the operator was wearing a single layer of cotton overalls.
- When a low-pressure hand wand was used, the MOE value for prosulfuron was acceptable when a single layer of PPE with gloves was used.
- After use of the products (at the proposed use pattern and use rates), MOEs for worker re-entry to treated areas are acceptable for low-exposure activities on the day of spraying (i.e. after the spray has dried on day zero).

XXXXX

Applicant's Response to the Evaluation Report

The applicant had seen a copy of the evaluation report and had informed the evaluator that they had no comments on the scheduling proposal provided by the evaluator.

October 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORYCOMMITTEE DISCUSSION

XXXXX

Members agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits of the substance; (c) toxicity; and (d) dosage and formulation of the substance.

Active

Members first considered the appropriate scheduling for a prosulfuron parent entry. Members noted that due to low acute toxicity, several sulfonylurea substances were listed either in Appendix B or Schedule 5. Several Members, however, noted that prosulfuron's toxicity was different from other sulfonylurea substances and asserted that, due to prosulfuron's moderate to high acute toxicity and carcinogenicity potential, a Schedule 6 listing would be appropriate.

Members then discussed the carcinogenicity concerns in more detail. A Member particularly raised concerns regarding the statistical interpretation of the female mammary gland carcinoma studies from the evaluation report. The Member asserted that the statistical interpretation was not comprehensive and lacked scientific rigour. Other Members raised concern regarding the testicular carcinoma study where the survival rate in the group exposed to prosulfuron was significantly higher that that of the control group. A Member indicated that the long-term study assessing potential carcinogenicity was questionable and the study was not comprehensive therefore there was greater uncertainty regarding the carcinogenic potential of prosulfuron. Members noted the uncertainty relating to carcinogenicity from the evaluation report and agreed that this warranted a precautionary approach supporting a Schedule 6 entry.

Another Member also noted that while the US EPA classified prosulfuron as "Not Likely to Be Carcinogenic to Humans", this classification was based on a lack of evidence of carcinogenicity in male and female mice at the limit dose and equivocal evidence of carcinogenicity in female rats. In female rats, there was suggestive evidence of a possible treatment-related increase in the incidence of adenocarcinomas of the mammary glands at the mid dose but not at the high dose. The report stated that "this lack of dose-response (i.e. the relatively limited response in the high dose group and a more pronounced response in the middle-dose group) along with the lack of evidence of carcinogenicity in mice and the lack of evidence for *in vivo* or *in vitro* mutagenicity lowered the concern for the carcinogenic potential of prosulfuron".

Cut-off

Members also discussed whether there was sufficient justification from the product data to support the evaluator's recommendation of a cut-off to Schedule 5 for preparations containing 5 per cent or less of prosulfuron.

A Member noted that, despite the current limited use addressed in the evaluation report which did not include use on food crops, prosulfuron was registered overseas for use in food crops. The Member was therefore concerned that there was potential for off-label use on food crops which could lead to higher risks than identified through the MOE calculations. The Member argued that this was yet another reason to support Schedule 6 with no cut-off. A Member disputed this being the basis for no cut-off, asserting that prosulfuron had been used in these countries for a considerable time and these countries have had sufficient exposure and experience to this chemical to determine its inherent properties and resulting safety aspects. However, as the condition of use differs greatly among countries and as a new substance and new product in the Australian context, Members generally agreed that a conservative approach should be taken.

Members also reiterated that given the lack of comprehensive information regarding the carcinogenicity endpoint, a lower concentration cut-off to Schedule 5 at 5 per cent or less prosulfuron would not be appropriate at this time.

XXXXX

Implementation

The Committee agreed that there were no matters which would require a delayed implementation period for this decision.

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 also agreed that an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012) was appropriate.

The relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits of the substance; (c) toxicity and (d) dosage and formulation of the substance.

DELEGATE'S INTERIM DECISION

The delegate decided that a new Schedule 6 entry be created for prosulfuron. The delegate also decided that a lower concentration cut-off to Schedule 5 listing at 5 per cent or less of prosulfuron was not appropriate. The delegate decided an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

Schedule 6 – New entry

PROSULFURON.

1.6 DICAMBA

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Dicamba – seeking advice regarding the appropriateness of the current scheduling of dicamba. In particular, whether the current 20 per cent cut-off from Schedule 6 to Schedule 5 could be increased; including, but not limited to, advice on a proposed increase of this cut-off to 50 per cent.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

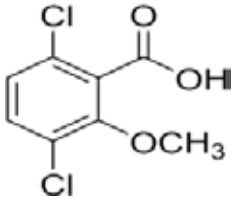
The Committee recommended that the current dicamba scheduling remained appropriate (i.e. no change).

BACKGROUND

Dicamba is a benzoic acid selective herbicide. The mode of action is by mimicking naturally occurring plant growth hormones called auxins. Dicamba affects cell wall integrity and nucleic acid metabolism, and kills plants by destroying tissue through uncontrolled cell division and growth. Dicamba uptake occurs by the roots, stems and foliage.

Dicamba can be applied to the leaves or to the soil. Dicamba controls annual and perennial broadleaf weeds in grain crops and grasslands, and brush and bracken in pastures. In combination with a phenoxyalkanoic acid or other herbicides, dicamba is also used in pastures, range land, and non-crop areas such as fence-rows and roadways to control weeds.

The IUPAC name for dicamba is 3,6-dichloro-2-methoxybenzoic acid and the structure is:



Dicamba's first scheduling (in Schedule 5), predates the early 1970's. In May 1986, the Drugs and Poison Scheduling Committee (DPSC) considered a review of Industrial Bio-Test Laboratories' (IBT) toxicology studies. This review was triggered as the fact that the IBT was found to have systematically falsified product safety test data. Members were of the opinion that there was nothing to indicate that the existing Schedule 5 status of this substance should be altered.

In February 1991, the DPSC considered an evaluation of a chronic dietary study in mice and genotoxicity studies for dicamba. The chronic study showed reduced weight gain, increased mortality, increased lymphocyte/neutrophil ratio, with no evidence of carcinogenicity. Dicamba induced single strand breaks in DNA, increased sister chromatid exchanges (SCEs) in human lymphocytes and was positive in an Unscheduled DNA Synthesis assay using human lymphocytes. Previous genotoxicity and carcinogenicity assays were clear. The DPSC agreed that the genotoxicity findings were equivocal and their significance were unclear and decided not to change the scheduling of dicamba.

In February 1997, the NDPSC considered toxicological data relating to dicamba and foreshadowed that dicamba would be rescheduled from Schedule 5 to Schedule 6. Dicamba was noted to have a XXXXX, and to be corrosive to the rabbit eye and a skin sensitiser in guinea pig.

In May 1997, the NDPSC considered correspondence from a company requesting that no change be made to the scheduling of dicamba until it had the opportunity to generate data for consideration to support a cut-off from Schedule 6 to Schedule 5. The company advised that it intended to generate data for a product, containing 20 per cent dicamba (as the dimethylamine salt), the highest concentration in a registered product, in support of a cut-off to Schedule 5. The NDPSC recognised that there would be no regulatory impact if the foreshadowed proposal were to proceed and a cut-off to Schedule 5 at 20 per cent supported. However, in view of the commitment by the company to generate data on a 20 per cent product it was considered prudent to assess the data before finalising the decision.

In August 1997, the NDPSC noted advice from the same company that it would not be proceeding with a proposal to conduct an acute toxicological package for the product containing XXXXX dicamba. The Committee considered that the foreshadowed proposal should proceed and that there be a cut-off to Schedule 5 at 20 per cent.

XXXXX submitted data to the APVMA seeking XXXXX containing XXXXX dicamba. While the evaluation report did not make scheduling recommendation on dicamba, the delegate noted that the toxicity data on the product had been used as the basis for the reports XXXXX cut-off recommendation, and wished to investigate if the same argument may apply to dicamba.

SCHEDULING STATUS

Preparations containing 20 per cent or less dicamba are listed in Schedule 5 and all other concentrations are listed in Schedule 6.

INITIAL SUBMISSIONS

Members noted that this matter was a delegate initiated matter and a current, comprehensive XXXXX Risk Assessment Technical Report on dicamba's toxicology at

50 per cent or less was not available. The 2011 XXXXX evaluation report did have data submitted to APVMA in support XXXXX. The dicamba specific toxicology information in the evaluation report, however, was obtained from a XXXXX dicamba update completed in 1998 on the Technical Grade Active Constituent dicamba.

Toxicology

- The ADI for dicamba was established XXXXX based on a NOEL of XXXXX developmental study and using a 100-fold safety factor. No ARfD for dicamba was established.

Acute toxicity

- Dicamba had low oral toxicity XXXXX. Members noted that according to the SPF, the XXXXX acute oral toxicity end-point aligns with Schedule 6 factors. It had low dermal toxicity XXXXX
- While the evaluation report also indicated that skin irritation was seen at XXXXX, the evaluator subsequently clarified that this value was based on a study using 0.5 mL of dicamba and further information was not available.
- Acute inhalation of dicamba XXXXX produced toxicological signs (aberrant motor activity and nasal porphyrin discharge, and a few animals had corneal opacity) at doses of XXXXX, and induced deaths XXXXX. Deaths were accompanied by congestion of the lungs and the liver. Members noted that an inhalation LC_{50} value was not provided.
- Dicamba was corrosive to eyes of rabbits. Members noted that corrosive eye irritation aligns with the Schedule 7 SPF factors. However, no further details of these corrosive findings were available so Members were unable to confirm if this classification aligns with the Scheduling Policy Framework's definition of "irreversible tissue damage". Dicamba is a slight irritant to the skin of XXXXX, and caused moderate skin sensitisation in XXXXX (although no skin sensitisation was seen in another study in XXXXX).

Short-term repeat-dose studies

- Repeated dermal applications XXXXX produced dermal reactions even at the lowest dose tested XXXXX but did not produce any marked systemic toxicity.
- *Dermal toxicity*: XXXXX dermal toxicity study XXXXX dicamba was topically applied to dorsal skin XXXXX. The study report did not specify whether it was under occlusive dressing or exposure duration per day. Erythema was observed in all treated groups in a dose-dependent relationship in both intensity and duration: slight XXXXX at low dose, and moderate to severe XXXXX at high dose. Oedema, atonia, desquamation and fissuring also occurred in all treated groups again in a dose-dependent relationship. The evaluator indicated that no NOEL could be established in this study due to the findings observed in all treated groups.

- An inhalation study XXXXX revealed significant toxicity by this route, with XXXXX deaths after XXXXX exposures to 20 mg/L. Compound-related lesions included oedema and congestion in lungs and haemorrhagic foci in the stomach. Slight lung effects were seen with the XXXXX dose.
- *Inhalation study*: XXXXX inhalation study XXXXX were exposed to atmosphere containing approximately XXXXX. The evaluator noted that the following observations were considered treatment-related. At XXXXX animals died (mean deaths occurred on day XXXXX and all dead XXXXX exhibited a red-tinged nasal discharge. XXXXX exhibited red-tinged ocular discharge, eye squint, dyspnoea and a general weakness, and at XXXXX displayed a transient red-tinged nasal discharge. Body weights were depressed XXXXX. Fasting blood glucose values decreased in all exposure groups. Pathology examination revealed oedema and congestion or red colouration in the lungs of XXXXX had brown, red and/or haemorrhagic foci on the stomach mucosa were observed. Very slight to marked perivascular oedema was observed in the lungs of XXXXX, and in the lungs XXXXX.
- Short and long term repeat dosing of dicamba to laboratory animals caused reduced food consumption, lower body weights and liver toxicity.
- Neurotoxicity effects had been observed following a single dose (aberrant and decreased locomotor activity). The evaluator noted that a US National Pesticide Information Center factsheet (http://npic.orst.edu/factsheets/dicamba_tech.pdf) for dicamba indicated that a dietary 13-week subchronic neurotoxicity study in the rat resulted in rigid body tone and impaired walking and balance at 1029 mg/kg bw/d.
- There was no evidence of reproductive toxicity, developmental toxicity or carcinogenicity, and dicamba was not genotoxic *in vivo*.

Sub-chronic studies

- XXXXX dietary study XXXXX were given XXXXX dicamba in the diet. At the highest dose XXXXX, body weight gain and food consumption decreased, serum alkaline phosphatase (SAP) activity slightly increased, and glucose values significantly decreased. At pathology examination, sporadic increases in relative liver and kidney weights occurred XXXXX and were probably related to reduced body weights. Histopathology indicated reduced cytoplasmic vacuolation in hepatocytes of the two highest dose groups and appeared to be related to the reduced liver glycogen storage in these groups. The NOEL in this study was XXXXX

Chronic studies

- The evaluator noted that the chronic toxicity was examined in 4 studies, two of these, XXXXX (both in 1962) were old and poorly documented, while the third study XXXXX was declared by the US EPA to be invalid. Thus, only one study XXXXX (1985) and XXXXX (1962) are detailed below.

- In a non-guideline compliant XXXXX dietary study (1985) XXXXX were given XXXXX dicamba in the diet for XXXXX. No significant treatment-related toxicity was observed, except significantly increased relative kidney weight in the high dose XXXXX. There was a slight increase in malignant lymphoma (of the mixed type) in the mid and high dose XXXXX , but no corresponding tumours were found in the XXXXX. The increased incidence of the above tumours was not statistically significant. The evaluator indicated that it was questionable whether the tumours were treatment related. The NOEL in the XXXXX, based on increased relative kidney weight in XXXXX at the highest dose.
- In the non-guideline compliant XXXXX dietary study (1962) XXXXX were given XXXXX dicamba in the diet. Body weight gain appeared to be reduced in the high dose groups in both sexes. However, the situation was complicated by the fact that not all XXXXX achieved full maturation at 7 months (the beginning of experiment) and that XXXXX vary in size when fully grown. The evaluator noted that the study was considered not appropriate to evaluate the oncogenic potential of dicamba. The NOEL for this study XXXXX the highest dose tested.
- The evaluator noted that the above XXXXX studies were not satisfactory by the current standards. The doses do not appear to be high enough to cause any toxicity, and no urinalysis or blood chemistry was performed. The histology was presented together with incidence of neoplasms in the form of individual data tables – no summary was provided and the animals were not identified as belonging to any treatment groups.

Reproductive studies

- In a 3-generation reproduction study (1966) XXXXX, dicamba in the diet at up to XXXXX had no apparent effect on the fertility, the ability of pregnant females to bear live young or upon the viability of the progeny. The NOEL was XXXXX.
- Dicamba had no cumulative toxicity when fed to XXXXX. The compound exerted no effect on the fertility, ability to bear live offspring or upon the viability of the progeny. Growth of XXXXX was not affected by the compound. Dicamba was not teratogenic in this study.

Developmental studies

- Teratology studies were performed XXXXX. No anomalies which could be attributed to dicamba occurred in any of these two studies. The NOELs for maternotoxicity were XXXXX, respectively.
- In a developmental study XXXXX (number of animals/group was not provided), dicamba was dosed by oral gavage at XXXXX. Mortality occurred in high dose group, with XXXXX dying on or before the second day of dosing. Body weights were reduced in high dose group, accompanied by reduced food consumption in these XXXXX. Maternal toxicity in the high dose group was seen in form of ataxia,

stiffening of the body and decreased motor activity. Implantation rates, resorption rates and the number of foetuses were similar between treated and control groups. Foetal development, both external and internal, remained unaffected. There was a slightly larger number of foetuses with delayed ossification in the high dose group, but this was not significant and was probably related to the poor maternal condition. Two gross malformations were identified; one in the control group and one in the XXXXX group. The malformed control foetus had microphthalmia and the other had a shortened body. There were no other grossly altered structural abnormalities, nor soft visceral anomalies. Dicamba was not teratogenic in this study. The NOEL for maternotoxicity was XXXXX.

Genotoxicity studies

- Dicamba was not genotoxic in reverse mutation tests in bacteria or in a mitotic recombination tests in yeast, and did not induce unscheduled DNA synthesis in human fibroblasts. It was also not mutagenic in a *Drosophila* sex-linked recessive lethal test. Dicamba did produce differential toxicity in DNA repair of deficient and proficient strains of *E. coli* and *Bacillus subtilis*.
- Dicamba increased the unwinding rate of XXXXX liver DNA *in vivo*, induced unscheduled DNA synthesis in human peripheral lymphocytes *in vitro* (in contrast to the result with human fibroblasts), and slightly increased sister chromatid exchange frequency in human lymphocytes *in vitro*. Overall, dicamba appeared to be capable of binding to DNA but did not produce point mutations.

Toxicokinetics and Metabolism

- The metabolic fate of dicamba has been studied XXXXX. Dicamba was absorbed through the gut efficiently and quickly, remained largely unchanged and was excreted rapidly, predominantly in urine. No significant species differences occurred in the metabolism and excretion of this compound.

Hazard classification

Dicamba was listed on the Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database (SWA, 2009) with the following risk phrases:

Xn; R22	Harmful if swallowed
Xi; R41	Risk of serious eye damage

- The following cut-off concentrations apply for dicamba:

Conc. ³ 25%	Xn; R22 Harmful if swallowed R41 Risk of serious eye damage

10% £ Conc. < 25%	Xi; R41 Risk of serious eye damage
5% £ Conc. < 10%	Xi; R36 Irritating to eyes

Toxicology of the product XXXXX *dicamba*

- Members noted the toxicity profile on the product XXXXX dicamba and XXXXX

- The product containing XXXXX was of low acute oral and dermal toxicity, a slight eye and skin irritant XXXXX and neither a skin irritant XXXXX nor a skin sensitiser XXXXX.
- Eye irritation: in an eye irritation study, 0.1 mL of the test material was applied into the conjunctival sac of XXXXX. Apart from corneal opacity observations, discharge was only seen in the animals receiving local anaesthetic and these animals had a slightly higher conjunctival erythema at XXXXX. At XXXXX and XXXXX, the degree of conjunctival erythema was the same in all animals, as was its persistence (i.e. conjunctival erythema was reversible in all animals at XXXXX).
- The evaluator asserted that since corneal opacity was only seen in a single animal (that received anaesthetic) and not from XXXXX onwards, it was not considered sufficient evidence to demonstrate a moderate eye irritation potential. The evaluator further noted that this was supported by the severity of the only other effect seen, minimal to moderate conjunctival erythema which was reversible in all animals by 72 h. The evaluator concluded that the product exhibited a slight not a moderate eye irritation potential in this study.

Percutaneous absorption

- The evaluator noted that an *in vitro* and an *in vivo* dermal absorption study were submitted for the existing active constituent dicamba. The studies were conducted using a reference product XXXXX and were considered suitable or providing surrogate data for use in determining the percutaneous absorption of dicamba. Furthermore, the *in vitro* data was used to refine the XXXXX *in vivo* dermal absorption value to give a more accurate prediction of human exposure *in vivo* for use in the risk assessment. For dicamba, a dermal absorption rate of XXXXX for the undiluted product (i.e. mixer loader activities) and XXXXX for the diluted product (i.e. application activities) was used for risk assessment purposes.

Exposure

- The product was proposed to be used XXXXX
- XXXXX would be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, during application, cleaning up spills, maintaining equipment and entering treated areas. The main route of exposure

to the product during dilution and spray will be dermal, though inhalation and ocular exposure were also likely. The main concern with the product was a slight eye irritancy and this issue could be managed by the use of personal protective equipment.

- Based on the product use pattern, the use period would extend to no more than 6 weeks, and worker exposure was likely to be short term repeat use of the product during this period.
- The product was not intended for domestic use and would not be used in food-producing crops. Based on the hazard profile of both the active constituents and the product and the proposed use of the product as a diluted spray, the risks to the public from accidental exposure to the product from bystander overspray/spray-drift were expected to be low.
- The product may be used in publically accessible areas and the main route of public exposure would be via re-entry to treated areas. Although post-application exposure may involve high exposure-equivalent activities involving direct contact with treated turf while playing sport, such exposure was likely to be infrequent and limited in extent, and hence the risks were expected to be low. The evaluator recommended a re-entry statement indicating "*Do not allow the general public to enter treated area until the spray has dried*".

Margin of Exposure

- The following information is regarding margin of exposure (MOEs) for dicamba submitted with the XXXXX application. MOEs of 100 or above are considered acceptable and take into account both interspecies extrapolation and intraspecies variability.

XXXXX.

- The MOEs for ground-boom application were acceptable for dicamba when the operator was wearing a single layer of PPE with or without gloves. Therefore, this application method was not expected to pose an undue hazard to human health when the operator was wearing a single later of cotton overalls.
- When a low-pressure hand wand was used, the MOE value for dicamba was not acceptable when a single layer of PPE with gloves was used. An acceptable MOE for dicamba was only achieved with the use of a second layer of clothing and a respirator. Therefore, the product was expected to not be an undue hazard to human health when the operator was wearing cotton overalls over normal clothing, chemical resistant gloves and a respirator.
- For backpack application an acceptable MOE was not achieved for dicamba even with the use of a second layer of clothing (over normal clothing), a washable hat and a respirator.

- Acceptable re-entry MOEs for high-exposure activities, such as weeding by hand or transplanting, were not achieved until day 14 for dicamba. The evaluator therefore recommended the following re-entry statements:
  - *"Do not allow entry into treated areas until the spray has dried for low exposure activities such as mowing, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves. Clothing must be laundered after each day's use."*
  - *"Do not allow entry into treated areas for 14 days for high exposure activities such as hand weeding or transplanting, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical resistant gloves. Clothing must be laundered after each day's use."*

Applicant's Response to the Evaluation Report

As the matter was initiated by the delegate, there was no applicant.

October 2011 Pre-meeting Submissions

A public submission from XXXXX was received. The submission supporting the delegate's proposal to reschedule dicamba. XXXXX.

The submission provided the following:

The extent and patterns of use

- XXXXX
- XXXXX. Asserted that this aspect had also benefits of use in the home garden market and is routinely found in "weed'n'feed" formulations.
- XXXXX
- Asserted, that as the chemistry was fairly benign, supported the delegate's proposal.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members noted that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits; (c) toxicity and (d) dosage and formulation of the substance.

The Committee noted that the delegate had indicated that dicamba was considered by the NDPSC on several occasions and that the record of the NDPSC's decision, especially for the 20 per cent cut-off to scheduling at Schedule 5, appeared limited. The Committee considered the delegate's request for the ACCS's advice about whether the toxicity profile of dicamba warranted a broadening of the cut-off from Schedule 6 to Schedule 5, i.e. from 20 to 50 per cent.

Members generally agreed that although dicamba had low acute oral toxicity, its high inhalation toxicity and eye corrosive properties continued to warrant a Schedule 6 listing.

Members noted that except for MOE studies on a mixed active product, no recent, robust data had been presented to support reconsideration of the current Schedule 6 to Schedule 5 cut-off for dicamba. Members also noted that the dicamba's re-entry period, from the MOE studies, was significantly high (14 d) and another Member noted that the MOE values for low-pressure hand wand and backpack applications were unacceptable, especially for backpack applications where even with a second layer of clothing an acceptable MOE was not achieved.

Several Members noted the limited number of pre-meeting submissions and suggested that if the current scheduling cut-offs for dicamba were not appropriate, interested companies could submit data for further consideration of the scheduling of dicamba.

Members generally agreed that, due to its high toxicity potential and lack of robust data, a reconsideration of current low concentration cut-off was not appropriate.

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 relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* appear to include (a) risks and benefits of the substance; (c) toxicity and (d) dosage and formulation of the substance.

DELEGATE'S INTERIM DECISION

The delegate decided that the current dicamba scheduling remained appropriate (i.e. no change).

2. OCTOBER 2011 MEETING OF THE ADVISORY COMMITTEE ON MEDICINES SCHEDULING (ACMS) – ACMS#4

2.1 PROPOSED CHANGES TO PART 2 OF THE SUSMP (LABELS AND CONTAINERS)

2.1.1 SCHEDULE 8 LABELLING REQUIREMENTS

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Schedule 8 labelling requirements – seeking advice on a proposal to amend Part 2, subparagraph 7(1)(a)(iv) of the SUSMP to allow an appropriate designation under the New Zealand *Misuse of Drugs Regulations 1977* next to the signal word on the signal word line. This possible amendment may allow some common packaging to be used for Schedule 8 products between Australia and New Zealand. Advice is also sought on potential harmonisation of other SUSMP Schedule 8 general labelling requirements between Australia and New Zealand.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current labelling and packaging requirements for Schedule 8 substances remained appropriate.

Members also recommended that the delegate refer the issue of signal heading harmonisation to NCCTG.

BACKGROUND

Labelling and availability of controlled substances in New Zealand (NZ) is controlled through the *Misuse of Drugs Act 1975* (MODA). At the June 2003 meeting of the Trans-Tasman Harmonisation Working Party (TTHWP) a common Schedule 8 labelling scheme for Australian and NZ was endorsed.

In June 2003, the National Drugs and Poisons Scheduling Committee (NDPSC) considered the TTHWP decision and agreed to foreshadow an amendment to the SUSMP (then SUSDP) which was intended to achieve partial harmonisation in light of legislative differences between the two countries. The amendment would allow the NZ designation, as specified in NZ's MODA, to be included on the label of Schedule 8 medicines in Australia.

The foreshadowed amendment was considered in October 2003, where it was agreed to omit the letters "NZ" as their inclusion could lead to confusion and would not meet the requirements of the MODA.

In October 2004, the NDPSC considered comments received in relation to the foreshadowed amendment and agreed to proceed with the foreshadowed amendment.

In February 2005, the NDPSC noted that in November 2004, the National Coordinating Committee on Therapeutic Goods (NCCTG) considered options for harmonisation of signal headings. The NDPSC was advised that, in considering these options, NCCTG members noted the following:

- Australia had already made changes to the requirements on signal headings to align with the NZ *Medicines Act 1981*;
- Amending the scheduling standard to allow the NZ designated category for the MODA to be included on the signal heading line would not resolve the need for different signal headings for other medicines containing controlled drugs;
- These options could be seen as contrary to the intent of the then Australian and NZ Treaty to establish a single, bi-national agency to regulate therapeutic products;
- There were policy preferences that labels in Australia and NZ should be uniform; and
- NCCTG preferred the option of NZ reconsidering amending the MODA on order to maximise harmonisation of labels and signal headings. If NZ determined this was not possible, the matter should be referred to the Therapeutic Products Interim Ministerial Council for consideration.

The conclusion from the February 2005 NDPSC consideration therefore was that the then current Schedule 8 signal heading remained appropriate. Members noted that it was likely that NZ would instead be asked (by industry etc) to look at amending the MODA.

In June 2006, the NDPSC noted advice that the labelling of some Schedule 8 products still included the MODA designation on the same line as the words "CONTROLLED DRUG". The NDPSC noted that labelling was not harmonised and felt the presence of MODA labelling on Australian products was not appropriate.

In late June 2011, the Secretary of the Department of Health and Ageing announced the intent to establish a joint Australian NZ agency to regulate medicines, the Australia New Zealand Therapeutic Products Agency (ANZTPA).

XXXXX submitted an application seeking an amendment to Part 2 of the SUSMP to harmonise with NZ's labelling and packaging requirements for Schedule 8 products. This application was submitted direct to the Secretariat in compliance with the requirements for applications of this type. A delegate decided this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

The delegate also requested advice from the Committee and the general public on potential harmonisation of other SUSMP Schedule 8 general labelling requirements between Australia and NZ.

SCHEDULING STATUS

Australia's Schedule 8 labelling requirements are slightly different from requirements in NZ. Australia's Schedule 8 labelling, as per the SUSMP, requires that nothing be added on the line next to the signal wording "CONTROLLED DRUG". The only exception is for a Class label from the Australian Code for the Transport of Dangerous Goods by Road and Rail.

Conversely, under section 25 of the NZ *Misuse of Drugs Regulation 1977*, the signal wording "CONTROL DRUG" must be followed immediately by the appropriate designation (a letter and number code).

Applicant's Submission

XXXXX requested that the labelling requirement in Part 2 Labels and Containers for Schedule 8 preparations be amended to allow harmonisation of labelling and packaging between Australia and NZ.

The applicant made a number of points, as summarised below:

- Noted that one of the aims of the Australia New Zealand Closer Economic Relations Trade Agreement treaty was to eliminate barriers to trade between Australia and NZ. They asserted that the setting up of a joint pharmaceuticals regulatory system, however, was on hold. Members noted the ANZTPA announcement was made after the submission of this application.
- Noted that the SUSMP allows an exemption for Schedule 5 substances, with no apparent negative effects.
- Proposed the inclusion of the following new wording in Part 2, Labels and Containers:

  (iv) if the poison:

  (A) is a Schedule 5 poison, with nothing, other than a Class label as specified in the Australian Code for the Transport of Dangerous Goods by Road and Rail or a statement of the principal hazard of the poison, written on that line; or

  (B) is a Schedule 8 poison, with nothing, other than an appropriate designation as specified in the New Zealand Misuse of Drugs Regulations, written on that line; or

  (C) is not a Schedule 5 poison, or Schedule 8 poison, with nothing, other than a Class label as specified in the Australian Code for the Transport of Dangerous Goods by Road and Rail, written on that line;

- Asserted that the proposed amendment was not expected to change the current use of Schedule 8 substances and would facilitate the use of Australian Schedule 8 substances in NZ and vice versa.
- Indicated that the proposed amendment would improve inventory management and reduce supply problems, particularly for low volume products.
- Stated that the proposed amendment was not expected to substantially reduce the readability of the signal word.

The applicant also provided examples of current Australian and NZ Schedule 8 packages.

October 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that the relevant matter under Section 52E(1) of the *Therapeutic Goods Act 1989* was (d) the dosage, formulation, labelling, packaging and presentation of a substance.

A Member noted that the issue of harmonisation of Schedule 8 labelling had been considered by the NDPSC during 2003-2006 in the context of the formation of a joint Australian NZ agency to regulate medicines. Members noted that with the 2011 announcement of the formation of ANZTPA, this issue would again be raised.

A Member advised that the current proposed ANZTPA implementation program would start with the Therapeutic Goods Administration (TGA) conducting a business-to-business comparison. This program will also look at legislative changes to form a single agency. The Member stressed that this was envisaged as a long-term project and was unlikely to be examining specific scheduling harmonisation matters for some time. However, the Member also advised that the TGA had also initiated a review of labelling, including packaging requirements.

Members noted that in NZ, labelling was regulated by legislation and there were no current moves to change these requirements.

A Member noted that the applicant's argument that the SUSMP already allows for such an exemption for Schedule 5 products was misleading and asserted that this was a requirement rather than an exemption.

Members questioned to what extent these proposed changes could confuse pharmacists and consumers. A Member suggested that the key consideration was whether these changes to labelling could compromise public safety by making labelling less clear. It was noted that there was a lack of information to gauge the industry response to these

changes as no pre-meeting submissions were received. Members noted that the intent of the delegate's proposal had been to facilitate comments from industry on whether there were any other Schedule 8 labelling restrictions imposed by the SUSMP which prevented harmonisation between Australia and NZ.

A Member suggested it was unlikely this proposed change would create any significant concern amongst either industry or consumers and that any concerns could be alleviated by appropriate education. The Member therefore supported the change in principle, but noted that any change should be foreshadowed pending further consultation with peak bodies (such as the Pharmaceutical Society Australia), who may be willing to assist with disseminating information on the change.

Another Member, however, recalled the NDPSC considerations in 2006, where one company had introduced common packaging for a product without seeking approval. This did create confusion amongst pharmacists, who mistook the NZ designation for some unknown scheduling status indicator. A Member suggested that there would need to be significant professional education if this change was approved.

A Member also noted that the current signal heading had been firmly established for 40-50 years. The Member opposed changing such well-established practices for the sake of harmonisation. The Member also raised concerns that such a move may open the floodgates for other information to be included in the signal heading line, which would lessen the already limited effectiveness of signal headings.

Members noted that in NZ, labelling was regulated by legislation and there were no current moves to change these requirements.

Members generally agreed that the proposed changes to the Schedule 8 signal heading requirements were a scheduling policy matter and as such this proposal should not proceed before consideration by the NCCTG.

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 matter under section 52E (1) of the *Therapeutic Goods Act 1989* was (d) the dosage, formulation, labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided that the current labelling and packaging requirements for Schedule 8 substances remains appropriate.

The delegate also decided to refer the issue of signal heading harmonisation to the NCCTG.

2.2 PROPOSED CHANGES TO PART 4 OF THE SUSMP (THE SCHEDULES)

2.2.1 AZELASTINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Azelastine – Seeking advice on a proposal to reschedule azelastine from Schedule 3 to Schedule 2 when supplied in topical eye preparations containing 0.05 per cent or less of azelastine.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended the down scheduling of azelastine when in topical eye preparations containing 0.05 per cent or less from Schedule 3 to Schedule 2. The Committee also recommended the deletion of the Appendix H entry for azelastine.

The Committee agreed on an implementation period of no more than six months after the final delegate's decision (i.e. 1 May 2012).

BACKGROUND

Azelastine is an antihistamine H1-receptor antagonist initially developed as a tablet formulation for the prophylaxis and treatment of allergic rhinitis and bronchial asthma and marketed as tablets and granules in Japan since 1987. It was also available in some European countries and Korea in different strengths and dosages.

An intranasal formulation was subsequently developed for seasonal and perennial allergic rhinitis. This formulation has been available in the UK since 1997, without prescription in adults and more recently extended to include children and perennial allergic rhinitis it is also available in the US, Australia and New Zealand.

The eye drop formulation was registered in the EU/UK in 1998, initially for seasonal allergic conjunctivitis in adults and children aged 12 years and over, then in children aged 4 years and over from 1999. Azelastine eye drops are currently licensed in more than 50 countries worldwide including New Zealand and the US.

In May 2000, the NDPSC decided to include azelastine in Schedule 4 with an exemption to Schedule 2 for preparations for nasal use.

An OTC switch from prescription only status for azelastine eye drop was granted in 2002 in Denmark, and subsequently in the UK, Germany and Switzerland.

In February 2006, the NDPSC considered an application to reschedule azelastine in topical eye preparations (0.05 per cent or less of azelastine) from Schedule 4 to Schedule 2. The NDPSC, however, decided to include azelastine in Schedule 3 to allow the opportunity for greater pharmacist and consumer familiarity with use in Australia. The NDPSC also agreed that the product did seem to fit Schedule 2 requirements though there was no local market experience at the time.

XXXXX submitted an application in support of rescheduling azelastine direct to the Secretariat in compliance with the requirements for applications of this type. A delegate agreed that this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

SCHEDULING STATUS

Azelastine in topical eye preparations containing 0.05 per cent of less of azelastine is listed in Schedule 3. Azelastine in preparations for nasal use is listed in Schedule 2. All other azelastine preparations are captured by Schedule 4. New Zealand restrictions on azelastine are equivalent.

INITIAL SUBMISSIONS

Applicant's submission

XXXXX requested rescheduling azelastine when in topical eye preparations containing 0.05 per cent or less of azelastine from Schedule 3 to Schedule 2.

The application made a number of points, as summarised below:

- Azelastine was available in ocular preparations containing 0.5 mg/mL azelastine (0.05 per cent) with 0.125 mg/mL of benzalkonium chloride and 0.5 mg/mL of disodium edetate as antimicrobial preservatives.
- Asserted that the product has been available in Australia since April 2009 without any regulator imposed conditions, sanctions or other post market compliance requests.
- Azelastine eye drops have been approved to be marketed in more than 58 countries and the product was marketed in 50 countries for ocular use for the treatment and prevention of the symptoms of allergic conjunctivitis.
- The submission concluded that azelastine:
    - Presented as an ocular preparation was well established in the Australian and the international market.
    - Treatments with azelastine (72 per cent) and levocabastine (71 per cent) were superior to the placebo treatment (41 per cent) and no statistically significant difference was found between the azelastine and levocabastine groups.

- Eye drops compared positively with nine other products approved for same or similar indications existing in Australia (most recent, ketotifen 250mg/mL in 2008).
- Eye drops provided a very low risk, effective treatment for the relief of the approved indications – seasonal allergic conjunctivitis and non-seasonal (perennial) allergic conjunctivitis indications

The applicant also provided a number of specific arguments against Section 52E criteria, including:

a) Risks and Benefits

· Asserted that there were few hazards associated with azelastine and these were non-serious and transient in nature.

· Indicated that in the 0.05 per cent eye drop dose form, the systemic absorption of azelastine, even following long term administration of eye drops, led to low plasma concentrations of azelastine and therefore adverse events related to systemic plasma levels of the compound were unlikely to occur.

· Stated that in a double-blind, randomised, placebo-controlled, parallel group study adverse drug reactions were reported by 14 and 24 patients receiving 0.025 per cent and 0.05 per cent azelastine eye-drops, respectively, and by eight placebo patients. [Members noted that the applicant did not provide a copy of the study reference, nor was the size of the study group described in the application.] These reactions were mainly slight application site reactions and taste perversion (bitter or unpleasant taste). The study concluded that azelastine eye drops were effective and well tolerated at a dose of 0.05 per cent for the treatment of seasonal allergic conjunctivitis.

· Asserted that severe or prolonged consequences appeared unlikely. This was supported by an apparent lack of such consequences during clinical studies and post market experience.

b) Purpose and extent of use

· The product Eyezep Eye Drops was approved for the treatment and prevention of symptoms of seasonal and non-seasonal (perennial) allergic conjunctivitis in adults and children 4 years and above.

· Asserted that as a second generation antihistamine, azelastine was also a potent anti-allergic compound with histamine H1-receptor antagonist activity, a rapid onset (within 10 to 20 minutes) and long duration (up to 12 hours) of action and provided anti-inflammatory effects.

· Stated that since second-generation antihistamines became available, the treatment options for allergic conjunctivitis conditions had markedly expanded. This could be attributed to the maintenance of the efficacy of previous generations of

antihistamines, coupled with a more favourable safety profile and fewer adverse effects. These newer agents reduced application frequency and had the advantage of rapid therapeutic onset.

c) Toxicity and safety

- Stated that the approved Product Information (PI) contained data detailing the toxic effect of induced high doses of azelastine in pre-clinical studies in mice and rats.
- Asserted that the potential for toxicity from use of the topical eye preparation could be seen to be minimal given the formulation contains 0.05 per cent or less of azelastine.
- Indicated that azelastine demonstrated no carcinogenic potential in mice and rats at dietary doses up to 25 and 30 mg/kg/day respectively. Azelastine demonstrated no genotoxic potential in standard assays for gene mutations, chromosomal damage and DNA damage.
- Noted that in male and female rats, azelastine at oral doses of 30 mg/kg/day and more (over 3 orders of magnitude higher than the maximum recommended clinical dose on body surface area basis) caused a decrease in the fertility index, but in long-term toxicity studies up to two years there were no drug related alterations in reproductive organs either in males or in females in this species. Further indicated that a clinical study in 21 healthy human females using an intranasal dose of 1.12 mg/day azelastine found no effect on ovulation or sexual hormone pattern.

d) Dosage, formulation, labelling, packaging and presentation

- Asserted that the proposed patient education and counselling provided by the pharmacist at the point of sale combined with the instructions on the pack and in the CMI would provide a strong foundation for quality use of the medicine by a consumer.

e) Potential for misuse/abuse

- Indicated that it was not aware of any reports locally or internationally of overdose, misuse or abuse either by deliberate or accidental method. Further stated that no potential existed for diversion of azelastine eye drops into a Schedule 8 or prohibited substance.

f) Other matters

- Noted that nine other topical eye preparations approved in Australia with the same or similar indications as the 0.5 per cent azelastine topical eye preparations were currently listed in Schedule 2.
- Argued that azelastine eye drops fit the Schedule 2 criteria and this consideration was similar to the 2008 decision to reschedule ketotifen as a Schedule 2 ocular preparation. Member noted that in October 2008, the NDPSC decided to down-

schedule ketotifen 0.025 per cent or less for ophthalmic use to Schedule 2. The NDPSC specifically noted that:

- the systemic side-effects of the ketifofen preparation were commensurate with the condition i.e. seasonal allergic conjunctivitis; and
- its safety was comparable to other treatments for seasonal allergic conjunctivitis listed in Schedule 2.

Evaluation Report

The evaluator indicated that azelastine 0.05 per cent eye drops met the Schedule 2 criteria and supported the rescheduling from Schedule 3 to Schedule 2. The evaluator also provided specific discussion on several matters, including:

Usage

· Since April 2009, there had been XXXXX units sold in Australia and approximately XXXXX patients may have been exposed (the evaluator noted that this figure allowed for stock still in the supply chain).

Australian adverse reaction reporting

· Stated that the applicant received one report that resulted in "case line listing" in the Periodic Safety Update Report (PSUR) in Australia. The patient developed shivers, nausea, flu-like symptoms, diarrhoea and heartburn.

· Noted that "current approved PI identifies all reported ADRs for this case line listing and are listed as non-serious adverse events".

· Further noted that the PI did not have information on flu-like symptoms (not synonymous with "upper respiratory tract infection"), diarrhoea or heartburn.

· Contended that the Company Core Data Sheet (CCDS) included in the PSUR was even less comprehensive.

· Indicated that there had not been any reports to the TGA's Office of Product Review (previously ADRAC) of suspected adverse reactions to azelastine eye drops and asserted this was reasonably reassuring for the safety profile of the product assuming XXXXX individuals had been exposed to this product.

PSUR XXXXX

· Stated that the information in the PSUR was generally not cumulative, except when in-depth reviews of possible association with specific adverse effects were presented.

· The PSUR noted that, although the eye drops had marketing authorisation in 58 countries, they were actually marketed in about 50 of those countries. The report also noted that "No change of the Reference Safety Information or other safety action was considered necessary". The evaluator indicated that the applicant should confirm

whether this included that "no action has been taken by a regulatory authority for a safety reason".

- There were XXXXX medically-confirmed adverse reaction reports from worldwide sources. Of these XXXXX were classified as serious and XXXXX non-serious. The XXXXX serious reports described a heterogeneous group of effects, including where one patient had facial numbness and one patient had aggravation of asthma and other more direct effects on the eye. The evaluator noted that the applicant proposed to maintain continuous monitoring for reports of "decreased visual acuity" for which there had been XXXXX serious report and regarded this as an appropriate way forward.
- The evaluator indicated that there were no newly analysed clinical studies of azelastine topical eye preparations during the reporting period for this PSUR.

Addendum to the PSUR XXXXX

- Noted that this PSUR indicated that "No change of the Reference Safety Information or other safety action is considered necessary".
- There were XXXXX medically-confirmed case reports from worldwide sources, of which one report mentioned XXXXX adverse reaction terms graded as serious and not mentioned in the CCDS. Additionally there were XXXXX case reports from consumer/patients, XXXXX per cent of which were received from the US. The evaluator asserted that none of these were graded as serious.
- Indicated that, despite a request, the sponsor was not able to provide appendices to this addendum. Therefore it was not possible to review the line listing of individual reports, and consequently it was not known whether the line listing of the Australian report mentioned above was included in the Addendum.

The evaluator also provided a detailed review of each of the individual references not included in the previous application. This detailed review reiterated points already addressed in the evaluator's broader discussion, as outlined above.

Applicant's Response to the Evaluation Report

The applicant did not provide a XXXXX to the evaluation report.

October 2011 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX and three pharmacists (identical form letters).

XXXXX

Believed that the proposed azelastine form met the Scheduling Policy Framework criteria for Schedule 2. Noted that there were several ocular anti-allergic products currently in Schedule 2. Therefore, supported the rescheduling of azelastine to Schedule 2.

XXXXX

Supported the rescheduling of azelastine. The submission asserted that as a dual-action antihistamine, topical ocular azelastine outperformed other Schedule 2 topical products in treating allergic conjunctivitis. The submission also indicated that azelastine:

- was well tolerated with minimal systemic absorption;
- had as good as or better safety profile than other Schedule 2 allergic conjunctivitis products; and
- allergic conjunctivitis should be managed in a manner to promote access to professional advice when required. A Schedule 2 medicine facilitates access without the requirement for direct pharmacist counselling associated with supplying Schedule 3 medicines.

The submission also provided specific arguments against Section 52E of the Act, as summarised below:

(a) risks and benefits

- Stated that as systemic absorption of azelastine from topical ocular preparations was minimal, it would be well tolerated, even in more vulnerable groups such as children and elderly patients.
- Argued that although more than 90 per cent of azelastine was metabolised by CYP3A4 and CYP2D6, and to a lesser extent by CYP1A2, the low plasma concentration of azelastine after ocular administration indicated a relatively low risk of drug interactions.
- Indicated that the most common adverse reactions were taste perversion and application site reaction. Although azelastine reached the tongue via the lacrimal duct after ocular installation and had a bitter taste, this had not reduced compliance in patients who regularly use topical ocular azelastine products.
- Noted that azelastine had a category B3 listing for safety in pregnancy, which indicates limited data regarding human use but studies in animals had shown evidence of an increased occurrence of foetal damage, the significance of which was considered uncertain in humans. Indicated that as a Schedule 2 product, this risk could be managed by appropriate labelling and referral to the pharmacist if needed.
- Argued that because absorption from the eye would be limited, azelastine would not be expected to cause any adverse effects in breastfed infants. Indicated that as a Schedule 2 product, this risk could be minimised by effective pharmacy assistant training and referral to pharmacists for advice when needed.

(b) purposes and the extent of use

- Noted that allergic conjunctivitis was common, affecting up to 40 per cent of the population. Indicated that allergic conjunctivitis was becoming more common and this may be due to various factors, such as increasing air pollution and cigarette smoking.
- Indicated that mild allergic conjunctivitis (acute, seasonal or perennial) represented up to 98 per cent of all cases of ocular allergy. The main symptoms of allergic conjunctivitis were itching of the eye and surrounding tissues, lacrimation (tearing), red eye, foreign body sensation and oedema of the eye lids. It was usually bilateral and associated with other conditions such as rhinitis.
- Noted that histamine was one of the mediators released by mast cells after specific allergen binding to the Immunoglobulin E (IgE) presented on the cell surface, contributing to the signs and symptoms of the immediate reaction characterising allergic conjunctivitis. Topical eye antihistamines were common treatments for allergic conjunctivitis.
- Asserted that the most widely used first generation ocular topical antihistamines were antazoline and pheniramine, administered in combination with vasoconstrictors to improve efficacy in providing symptom relief. Argued that several Schedule 2 topical vasoconstrictor-antihistamine combination preparations were currently available in which rebound conjunctivitis was a risk with long term use. With topical ocular vasoconstrictor use, it was recommended not to use regularly for more than 5 days. These products were contraindicated in people with narrow-angle glaucoma and caution was advised for elderly people and people with severe cardiovascular disease, uncontrolled hypertension, uncontrolled diabetes and people with urinary retention or prostate hypertrophy.
- Asserted that azelastine had been shown to effectively reduce allergic symptoms in patients suffering from seasonal allergic conjunctivitis, with a near maximal response after only 3 days of treatment.
- Noted that other Schedule 2 topical second-generation antihistamine products used for allergic conjunctivitis which have similar efficacy and safety profiles include levocabastine and ketotifen.
- Argued that as a second-generation antihistamine, azelastine had antihistaminic and anti-inflammatory properties. As a drug class, topical antihistamines with established dual action were very effective in treating allergic conjunctivitis and outperformed other groups of drugs such as mast cell stabilisers or topical eye non-steroidal anti-inflammatory preparations. Also argued it had not been possible to demonstrate that first-generation antihistamines offer anti-inflammatory-anti-allergic action in addition to their anti-pruriginous effects.

(d) dosage, formulation, labelling, packaging and presentation

- Stated that since the conjunctiva is an accessible mucosa, topical eye application was an ideal approach for the treatment of allergic conjunctivitis, since rapid action was assured, with improvement in eye hydration.
- Indicated that the risks associated with use in pregnancy or inappropriate use could be ameliorated by including the following warnings on the label:
  - "Do not use if pregnant"; and
  - "If symptoms persist, seek advice from a health care practitioner."
- Indicated that in addition to appropriate label warnings, pharmacy assistants were also trained to determine if referral to a pharmacist for professional advice was needed.

(f) other matters in public health interest

- Argued that non-pharmacologic interventions including strategies to reduce exposure to inciting antigens, management of dry eye and even dietary intervention were essential components in the care of patients with ocular allergy. Stated that inclusion of topical eye preparations in Schedule 2 promoted access to intervention from pharmacists if required to assist with pharmacologic and non-pharmacologic advice.
- Indicated that while Schedule 3 was more effective in facilitating pharmacist intervention, it can have a significant impact on pharmacist workflow. Asserted that mandatory pharmacist intervention was warranted when there were safety concerns or difficulties in patients being able to differentiate conditions from the presenting symptoms. Otherwise, for products with a good safety profile and proven efficacy for non-serious conditions with easily identifiable symptoms, pharmacy assistants were capable of supporting the supply of Schedule 2 products with referral to the pharmacist when needed.
- Also indicated that pharmacy assistants must complete appropriate training regarding Schedule 2 and Schedule 3 medicines as part of the Quality Care Pharmacy Program (QCPP) accreditation.

Pharmacists (identical form letters)

Three identical submissions stated that the proposed azelastine form meets the criteria for Schedule 2, similar to nine other Schedule 2 topical eye preparations approved for same or similar indications. Also noted that azelastine presented in this form had been approved and available for over two years on the Australian market. The submissions concluded that based on the quality use of medicines and the availability of topical eye preparation, they supported the rescheduling application.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that 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 (d) the dosage; formulation and presentation of a substance.

Members discussed aspects required to fit a Schedule 2 listing, including the azelastine market experience as an OTC product in Australia, and the use and safety profile of azelastine. Members agreed to the evaluator's recommendation to down schedule azelastine in topical eye preparations (0.05 per cent or less of azelastine) from Schedule 3 to Schedule 2. A summary of the discussion is provided below:

- Members noted the 2006 NDPSC consideration and reasons for inclusion of azelastine topical eye preparations in Schedule 3 largely focused on the lack of Australian OTC market experience. Members noted that since then azelastine topical eye preparations have had several years of Australian OTC market experience with no significant concerns arising.
- A Member stated that azelastine was widely available overseas with a good safety record, with few AE reported globally. The Member stated that these included some flu-like symptoms which were probably unrelated to azelastine.
- Members noted that azelastine in eye preparations were prescription only medicines (POM) in the UK. A Member noted that there are no antihistamines in eye preparations available OTC in the UK.
- A Member noted that azelastine was classified as pregnancy category B3. The Member questioned, however, the applicability of results of systemic effects which came from animal pregnancy studies using high doses of azelastine, given the low systemic absorption from the eye formulation. The Member also noted a recommendation from a pre-meeting submission for a labelling with a warning statement on use during pregnancy. The Member questioned whether such a statement was already included on current azelastine Schedule 3 labelling. Another Member advised that any medication classified above pregnancy category A would have TGA imposed label warnings. Another Member also asserted that the risks to the fetus may not be as great as any risk to the patient, as the exposure to azelastine from the eye drop formulation would be low.
- A Member noted that the majority of antihistamine eye drop preparations were Schedule 2 substances. Some Members were, however, concerned that if azelastine was in Schedule 2, supply would rely on pharmacy assistants, and questioned whether assistants would be able to appropriately advise and address matters related to the use of azelastine in pregnant women. A Member was also concerned that the appropriate use of Schedule 2 azelastine eye preparations would be up to the patient's own judgement. However, Members noted that the Pharmacy Guild provides training and information material to assistants on such matters.

- There was some concern among Members about whether pharmacy assistants would be equipped to diagnose allergic conditions. A Member made a comparison with chloramphenicol (Schedule 3) where a professional is needed to make a diagnosis and to differentiate between bacterial and viral infections, to ensure appropriate treatment. The Member stated that if azelastine is included in Schedule 2 it would be up to the pharmacy assistant to diagnose allergic versus viral or bacterial infection in patients. A Member contended, however, that there were a number of anti-allergy topical eye preparations in Schedule 2, and consumers were likely to discern an allergic reaction from a bacterial infection. The Member also stated that although misdiagnosis would cause some delay in symptoms cessation, this did not appear to be of significant concern. Members generally agreed that due to the safety profile of azelastine this would not result in a safety issue.

Members also discussed appropriate implementation timeframes for this decision. Members agreed that there were no impediments in implementing Schedule 2 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) the purpose and extent of use; and (d) the dosage; formulation and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to reschedule azelastine when in topical eye preparations containing 0.05 per cent or less from Schedule 3 to Schedule 2. The delegate also decided to delete the Appendix H entry for azelastine. The delegate decided that an implementation date of 1 May 2012 was appropriate (i.e. three months after the publication of the delegate's final decision).

Schedule 2 – Amendment

AZELASTINE – Amend entry to read:

AZELASTINE:

(a) in preparations for nasal use; or

(b) in topical eye preparations containing 0.05 per cent or less of azelastine.

Schedule 3 – Amendment

AZELASTINE – Delete entry.

Schedule 4 – Amendment

AZELASTINE – Amend entry to read:

AZELASTINE **except** when included in Schedule 2.

Appendix H – Amendment

AZELASTINE – Delete entry.

2.2.2 DICLOFENAC

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Diclofenac – Seeking advice on a proposal to exempt from scheduling dermal preparations containing diclofenac, other than those indicated for the treatment of solar keratosis. Advice is also being sought on two alternative approaches to this possible exemption from scheduling:

- limiting this possible exemption to preparations containing 4 per cent or less of diclofenac, other than those for the treatment of solar keratosis; or
- an exemption for topical preparations containing 2 per cent or less diclofenac and including in Schedule 2 topical preparations containing more than 2 per cent, up to 4 per cent diclofenac, when not indicated for the treatment of solar keratosis.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended rescheduling to Schedule 2 for dermal preparations containing more than 1 per cent up to 4 per cent or less of diclofenac, except when for the treatment of solar keratosis. The Committee also recommended a Schedule 4 entry for products containing more than 4 per cent diclofenac. The Committee confirmed that preparations containing 1 per cent or less of diclofenac would remain unscheduled and that preparations for use in solar keratosis would remain Schedule 4.

The Committee also agreed to an implementation period of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Diclofenac, a phenylacetic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac exhibits anti-inflammatory, analgesic and antipyretic properties by inhibiting prostaglandin synthesis through inhibition of cyclo-oxygenase-1 (COX-1) and

COX-2. Diclofenac was predominantly used for the relief of pain and inflammation in various conditions including musculoskeletal and joint disorders, in the management of actinic keratoses, and fever.

Diclofenac was first included in Schedule 4 in March 1981.

In February 1997, the NDPSC decided to reschedule diclofenac dermal preparations (creams) containing 1 per cent or less of diclofenac from Schedule 4 to Schedule 2. The decision was based on the safety profile of a 1 per cent formulation and the then approved indications for use in readily recognised conditions (minor pain relief), which did not include treatment of solar keratosis.

In August 1999, the NDPSC considered recommendations from the Trans-Tasman Harmonisation working party to exempt diclofenac for dermal use. The NDSC agreed that the scheduling of diclofenac for dermal use remained appropriate.

In November 1999, the NDPSC agreed to defer a reconsideration of the scheduling of diclofenac in dermal preparations to a later meeting. In February 2000, the NDPSC considered additional safety data and agreed that dermal preparations of diclofenac should be exempt from scheduling. This consideration focused on diclofenac products indicated for minor pain relief. The use of diclofenac for the treatment of keratoses was not mentioned in the records.

In March 2011, following advice from the December 2010 ACMS meeting, the delegate decided to include all dermal preparations containing more than 1 per cent diclofenac in Schedule 4. The delegate stated that there was a lack of Australian safety data on dermal preparations of diclofenac in concentrations greater than 1 per cent. The delegate also indicated that a new scheduling consideration could be commenced should sufficient evidence of safety and benefit to the public become available.

XXXXX submitted an application requesting the rescheduling of diclofenac. A delegate agreed that this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

SCHEDULING STATUS

Diclofenac in preparations for dermal use is currently listed in Schedule 4 when used for the treatment of solar keratosis or when containing more than 1 per cent of diclofenac. Diclofenac in divided preparations for oral use containing 25 mg of less of diclofenac in a pack containing 30 or less dosage units are listed in Schedule 3, and 12.5 mg or less in a pack containing 20 or less dosage units in Schedule 2. In NZ diclofenac for external use is classified as General Sale.

INITIAL SUBMISSIONS

Application

XXXXX proposed the rescheduling of diclofenac topical preparations containing 4 per cent or less of diclofenac, **except** for solar keratosis use, from Schedule 4 to unscheduled.

A supplementary option was also proposed to expand the dermal use exemption from 1 per cent to 2 per cent or less and reschedule dermal preparations (**except** for solar keratosis use) containing more than 2 per cent up to, and including, 4 per cent into Schedule 2.

A number of general points were made in the application, as summarised below:

- Stated that its dermal preparation had been used by more than 38 million consumers worldwide for the relief of pain and inflammation in soft tissue injuries, rheumatoid arthritis and osteoarthritis. Referred to the Martindale monograph for the following dermal/topical diclofenac preparations:
  - *gels (diclofenac diethylamine) consisting of the equivalent of 1 per cent of diclofenac sodium for the local symptomatic relief of pain and inflammation;*
  - *plasters (diclofenac epolamine) used topically containing the equivalent of 1 per cent of diclofenac sodium for local symptomatic pain relief in ankle sprain and epicondylitis;*
  - *topical solutions of 1.6 per cent diclofenac sodium for the treatment of osteoarthritis in superficial joints; and*
  - *gel containing 3 per cent diclofenac sodium used in the management of actinic keratosis.*

Members noted that the following topical products were listed on the ARTG: topical gels containing 1.16 per cent diclofenac diethylammonium (equivalent to 0.93 per cent diclofenac) or 1 per cent diclofenac sodium (equivalent to 0.93 per cent diclofenac). Topical solutions containing 1.6 per cent diclofenac sodium were not listed on the ARTG).

- Martindale also identified the availability of a topical spray gel containing diclofenac sodium 4 per cent, with a dose of 4 or 5 sprays (32 or 40 mg of diclofenac sodium), up to a maximum of 15 sprays (120 mg of diclofenac sodium) daily. Asserted that several countries, including the UK have had the spray gel formulation available as an OTC product since 2004 XXXXX.
- Contended that the delegate's March 2011 reasons did not highlight that diclofenac for the management of solar keratosis required a dosing that was different from common pain and inflammatory conditions where treatment was only for up to 21 days.

- Emphasised that the Product Information (PI) and consumer medicine information (CMI) shows that 3 per cent diclofenac for solar keratosis was intended to be used for at least 60-90 days.

The applicant referred to the delegate's March 2011 decision to include dermal diclofenac in Schedule 4, and noted a number of arguments, summarised below:

- Stated that in December 2010, the ACMS noted that apart from one product for the management of solar keratosis, the ARTG did not list any other diclofenac products for dermal use containing more than 1 per cent diclofenac. Believed that, according to the ACMS, the proposed amendment to the Schedule 4 entry was not expected to inadvertently capture any other diclofenac preparations for dermal use.
- Contended that this did not take into account any XXXXX for higher strength diclofenac dermal preparations.
- Stated that there were XXXXX. Members noted that the delegate was aware of these XXXXX at the time of confirming the final decision in March 2011.
- Contended that because of the rescheduling, XXXXX for dermal preparations containing more than 1 per cent diclofenac XXXXX

Members noted for the identification of dermal formulations containing different concentrations of diclofenac, the following terms were used in the rest of this paper:

- diclofenac 1.16 per cent gel: means 1.16 per cent diclofenac diethylammonium (equivalent to 0.93 per cent diclofenac);
- diclofenac 1 per cent gel: means 1 per cent diclofenac sodium (equivalent to 0.93 per cent diclofenac);
- diclofenac XXXXX per cent spray: means XXXXX per cent diclofenac sodium (not listed in the ARTG, equivalent to XXXXX per cent diclofenac);
- diclofenac 3 per cent gel: means 3 per cent diclofenac sodium used in the management of actinic keratosis (equivalent to 2.8 per cent diclofenac);
- diclofenac XXXXX per cent gel: means diclofenac diethylammonium XXXXX per cent gel (equivalent to XXXXX per cent diclofenac); and
- diclofenac XXXXX per cent spray gel: means diclofenac sodium XXXXX per cent spray gel product (equivalent to XXXXX per cent diclofenac).

In addition, the following general comments were made by the applicant:

- Stated that evidence of safety and efficacy (indications other than for solar keratosis) that supported a cut-off value to allow exemption for dermal preparations containing 1 per cent or less of diclofenac has already been presented.
- Asserted that safety and efficacy data for products containing 3 per cent diclofenac for solar keratosis (current ARTG products) would have been evaluated by the TGA.

- Affirmed that during the approval process of higher strength diclofenac preparations, *XXXXX*
- Argued that while it was generally agreed that solar keratosis was a condition that required medical supervision, treatment of pain and inflammation had long been accepted as not requiring the same level of control.
- Advised that higher-strength dermal formulations were designed to achieve the same efficacy with less frequent daily applications compared to the currently marketed 1 per cent diclofenac preparations, thereby improving convenience without compromising on safety. Stated that higher strengths would also provide for new formulations to be available (e.g. transdermal patches, spray solutions, spray gel), thereby giving consumers wider choices in application formats.

The applicant also addressed several matters against section 52E, as summarised below:

(a) Risks and benefits

- Asserted that clinical studies confirmed that there was very low systemic exposure from dermal preparations up to 4 per cent diclofenac.
- Affirmed that safety data for the diclofenac diethylammonium 1.16 per cent gel provided additional reassurance that the benign safety profile demonstrated in a clinical development program for higher strength preparations would be reproduced in actual use.
- Stated that these findings support the concept of using short-term repeated applications of dermal preparations of diclofenac up to 4 per cent for the relief of pain, inflammation and swelling in soft-tissue injuries, localised forms of soft tissue rheumatism, and for the relief of pain of non-serious arthritis of the knee or fingers.
- The information on dermal diclofenac use was summarised as follows:

Contraindications

- Similar to other topical NSAIDs.

Precautions

- Should be applied only to intact skin. The preparation should not come into contact with the eyes or mucous membranes.

Interactions

- There were isolated reports of suspected interaction of dermal diclofenac with oral anticoagulants. The concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage.
- The mechanism of the interaction may involve enhanced bleeding from NSAID induced gastrointestinal ulceration or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs.

- Since systemic absorption of diclofenac from dermal applications was likely to be very low, such interactions were unlikely to occur when these products were used as recommended.

Pregnancy and lactation

- Pregnancy Category C applies to diclofenac. The labelling for the proposed higher strength dermal preparations contains advice to not use in the first months of pregnancy and not use at all in the last three months of pregnancy.

['*Category C: 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…*'.]

- Diclofenac is not recommended during breast-feeding.

Unwanted effects

- Dermal diclofenac is generally well tolerated and has a similar side effect profile to other topical NSAIDs such as ibuprofen.
- The adverse effects profile of the XXXXX per cent gel and the XXXXX per cent diclofenac spray gel was similar to those observed in 1.16 per cent gel. Pruritus, erythema, rash, or stinging may occasionally occur.

Overdosage

- Because of the manner in which the higher strength dermal diclofenac preparations were presented, the potential for overdose was very low.
- Significant systemic reactions resulting from improper use or accidentally ingested overdosage (e.g. in children) should be treated by the general measures employed to manage poisoning with NSAIDs.

Therapeutic index

- XXXXX

(b) Purposes and extent of use

· Internationally, there were topical diclofenac formulations and corresponding salts: gel (diclofenac diethylammonium, diclofenac sodium); cutaneous spray (diclofenac sodium); foam (diclofenac free acid) and patches (diclofenac sodium, diclofenac epolamine).

· The *XXXXX* per cent spray gel provides temporary relief of pain and inflammation associated with rheumatism, sprains, strains, tendinitis, burstis and sports injuries.

· Internationally, although diclofenac *XXXXX* per cent gel (diclofenac diethylammonium) had not yet been approved, there was a post-marketing experience

with diclofenac topical products from *XXXXX*. It is estimated that *XXXXX* patients were exposed to diclofenac diethylammonium.

- The acute soft tissue injuries were self-diagnosable and did not require medical intervention and any adjunctive therapy. Soft-tissue rheumatisms could be considered subchronic conditions which did not require medical diagnosis or only required initial medical diagnosis and the consumer did not require close medical management.
- The treatment duration for *XXXXX* per cent spray gel was recommended to be not more than 14 days and if there was no improvement in symptoms, to consult a doctor. Asserted that the short treatment duration would not mask any serious diseases.

(c) Toxicity and safety

- Asserted that diclofenac was a well known and well tolerated drug that has been marketed for almost 40 years, worldwide. Taken orally, it was well absorbed and was approved for OTC use at doses up to 150 mg / daily.

XXXXX per cent gel

- Reiterated that the toxicity and safety of dermal diclofenac preparations up to 1 per cent have been well established.
- Provided a table of AEs from a group of *XXXXX* patients.

XXXXX

- Clinical safety studies with XXXXX per cent gel suggested that phototoxicity, sensitisation, or irritation were unlikely when the product was used as directed.
- Asserted that XXXXX per cent gel was well tolerated topically and the systemic exposure to diclofenac was similar to 1.16 gel, and was expected to be considerably lower than after oral treatment.
- Claimed that no close monitoring of the patient was required for a short treatment period, making XXXXX per cent gel suitable for availability as an unscheduled preparation.

XXXXX *per cent spray gel*

- Claimed that a clinical study had demonstrated that the use of diclofenac XXXXX per cent spray gel used for 15 days did not cause gastric lesions.
- Asserted that frequencies of adverse events for diclofenac resembled those for placebo with the exception of the application site events. The evaluation report provides a detail discussion on safety findings.
- Also asserted that XXXXX per cent spray gel was well tolerated topically, and like 1.16 per cent gel, the systemic exposure to diclofenac was low and expected to be considerably lower than after oral treatment, therefore no close monitoring of the patient was required for a short treatment.

Post-marketing safety analysis

- Stated that NSAIDs administered topically penetrated slowly and in small quantities into the systemic circulation. The bioavailability and maximal plasma NSAID concentration were generally less than 5 and 15 per cent, respectively, compared with equivalent oral administration.

Overview of reported cases to the global safety database

- Claimed that the majority of individual case study report (ICSRs) were assessed as non-serious and presented nonspecific self-limiting adverse events.
- No safety trends had been identified that would necessitate an update of the established safety profile of topical diclofenac products greater than 1 per cent.
- Based on the extensive history of post-marketing use (over XXXXX patients) and the small number of reported ICSRs (mainly cutaneous in nature) the available post-marketing data confirm the relatively benign adverse event profile of topical diclofenac products greater than 1 per cent.
- Further details are provided under the Evaluation Report heading.

(d) Dosage, formulation, labelling, packaging and presentation

XXXXX

(e) Potential for misuse / abuse

- Claimed that 1.16 per cent diclofenac diethylammonium gel and other topical NSAID preparations have been available for more than 10 years in Australia and there has been no evidence of abuse or dependence for any of these formats.

Off-label use

- Asserted that as with all medicines, it was difficult to totally prevent off-label use. Claimed that the long history of use of the brand name for pain and inflammatory conditions, combined with the pack size and labelling would limit the potential for off label use in solar keratosis.

Evaluation Report

The evaluator did not support the proposal to exempt diclofenac dermal products containing up to, and including 4 per cent of diclofenac from scheduling, arguing that such a move would be premature. The evaluator instead recommended a Schedule 2 entry for products containing more than 1 per cent up to 4 per cent or less of diclofenac, **except** when for the treatment of solar keratosis. The basis for this recommendation was summarised below:

- The steady-state systemic bioavailability of the XXXXX per cent spray gel was about 2 per cent of oral diclofenac 50 mg taken three times daily (i.e. 150 mg oral daily). Target tissue concentrations, however, were higher with topical administration.
- The steady-state systemic bioavailability of the XXXXX per cent gel was about 4.5 per cent of an equivalent oral diclofenac dose.
- While publications reported *oral* diclofenac use associated with increased risk of adverse cardiovascular (CV) events, there were no studies directly implicating topical diclofenac preparations. The low systemic bioavailabilities of the XXXXX per cent spray gel and the XXXXX per cent gel would seem to greatly reduce any CV risk compared with oral use.
- Pre-clinical and clinical study summaries indicated that the XXXXX per cent gel and the XXXXX per cent spray gel had acceptable potential for irritation and were not sensitisers or photosensitisers.
- Summaries in the short-term clinical studies with the XXXXX per cent gel and XXXXX per cent spray gel suggested low incidences of local cutaneous reactions.
- Stated that as of 31 May 2011 there was no post-marketing experience with the XXXXX per cent gel as it had not yet been approved anywhere in the world.
- Analyses of post-marketing experience were not sufficient, as most of the summarised data did not distinguish between events with the 1.16 per cent gel and other presentations, including higher strength products. However, no special issues stood out. There was little evidence of interactions involving topical diclofenac and systemic medications.

The evaluator assessed the safety data presented in the application and particularly noted that:

- The documents in the application were well presented, however, it did not include individual study reports and detailed safety data for XXXXX per cent gel and XXXXX per cent spray gel products.
- Safety information from animal studies was limited to low systemic bioavailability, no or minor skin irritation and lack of sensitisation and photosensitisation.
- While the applicant provided inferences about safety of dermal use when compared with plasma and tissue concentrations following oral use, the important data would be from local tissue bioavailability, to support the rationale for the development of diclofenac products for dermal use.
- From the microdialysis data, topical application was superior to oral administration in terms of higher concentrations in the peripheral target tissues and reduced systemic load, despite plasma concentrations that were about 2 per cent of those produced by oral administration. A similar microdialysis study was not included in the animal data for XXXXX per cent gel.

- A study that compared the systemic (plasma) concentrations following applications to the skin of similar doses of the 1.16 per cent gel and the XXXXX per cent gel, showed that the XXXXX per cent spray gel was less bioavailable than the 1 per cent gel, however, the number of subjects were very small.
- A pharmacodynamic study with 120 mg / day topical diclofenac, XXXXX per spray gel, 200 mg / day oral celecoxib, 1000 mg / day naproxen, and placebo in patients with acute gastro-duodenal injury, demonstrated that the use of diclofenac XXXXX per cent spray gel for 15 days had a very low association with gastric erosions (less than placebo in this study).
- Although the applicant claimed that XXXXX per cent gel was a mild product with no sensitisation and no clinically significant cumulative irritation potential, the detailed results were not available in the application.
- No long-term studies reported with XXXXX per cent gel or the XXXXX per cent spray gel.
- A Phase I local tolerability and Phase III tolerance study demonstrated that XXXXX per cent spray gel had similar very mild irritancy to the marketed 1.16 per cent gel. Only 3.2 per cent of those enrolled (2/62) were discontinued due to dermal reactions.
- A 21-day cumulative irritation study compared the irritancy potential of the XXXXX per cent spray gel with marketed reference products Arthricare For Women Multi-Action®, and Speed Stick® Regular Deodorant. The frequency of subjects discontinuing treatment was lowest for the diclofenac spray (35 per cent) compared to Speed Stick (49 per cent) and Arthricare (95 per cent).
- The applicant states that the daily maximum dose equivalents of diclofenac sodium were in the same range for the XXXXX per cent spray gel (120 mg) and the 1 per cent gel (160 mg). The submitted post-marketing experience was considerably influenced by the 1 per cent gel, which has a longer history of marketing. The Periodic Safety Update Reports for XXXXX per cent spray gel, including a report covering XXXXX were not included in the application documentation.
- Asserted that the National Pharmacovigilance data from Finland from XXXXX, were not of assistance as they include oral, rectal and parenteral use as well as topical use. Only one of XXXXX spontaneous reports related to an externally applied product.
- The applicant's global safety database XXXXX of XXXXX reports associated with topical diclofenac products stated that the most frequently clinical events were application site: erythema XXXXX, pruritus XXXXX and rash XXXXX The most frequently reported events in the skin and subcutaneous were dermatitis contact XXXXX erythema XXXXX pruritus XXXXX and rash XXXXX. The evaluator argued that the applicant should explain the method of calculation of the events as percentages. If XXXXX events represent XXXXX per cent of all events, there must have been a total of XXXXX events. The applicant responded that these XXXXX individual case safety reports (ICSRs) described a total of XXXXX events. The

applicant confirmed that XXXXX ICSR of erythema represents XXXXX per cent of all reported events.

- In relation to the overdose with topical preparations, including use on children less than 12 years of age, the applicant referred to the adequacy of information in the International Corporate Core Safety Information. The evaluator noted that this document was not provided in the application.
- The evaluator accepted that if used according to directions, withdrawal or rebound effects were unlikely, that the product should not be used in pregnancy (including the third trimester because of a possible effect on the ductus arteriosus), and that available information did not link the products to specific foetal defects or congenital anomalies.
- Available clinical studies suggested, but did not document, equivalent efficacy of topical over oral NSAIDs in rheumatic diseases. Reported that gastrointestinal adverse drug reactions were rare with topically applied NSAIDs, compared with a 15 per cent incidence reported for oral NSAIDs.
- Noted that a published review of the safety profile of topical diclofenac revealed that two authors received consultancy payments from the applicant. The study involved a systematic review to evaluate the risks of adverse events with topical diclofenac for acute and chronic musculoskeletal conditions.
- Asserted that 16 of the 37 studies were of the 1.16 per cent diethylamine diclofenac gel, and most of the other preparations were 1 per cent diclofenac gel. Contended that there were only three studies involving higher strength gels, including 2 per cent diclofenac lecithin organogel, 1.3 per cent diclofenac epolamine lecithin gel and 3 per cent diclofenac sodium in 2.5 per cent hyaluronan gel. Argued that none of the studies involved use of the XXXXX per cent diclofenac diethylamine gel or the XXXXX per cent diclofenac spray gel.

Applicant's Response to the Evaluation Report

XXXXX response addressed matters raised by the evaluator, and is summarised as follows:

- Agreed with the evaluator's conclusion supporting the rescheduling of preparations for dermal use containing more than 1 per cent of diclofenac to Schedule 2. Requested a confirmation whether the cut-off limit for dermal products in Schedule 2 would be preparations containing XXXXX per cent or less of diclofenac. [Members noted that the evaluator had confirmed that the recommendation was to include dermal products in Schedule 2 containing more than 1 per cent up to 4 per cent or less of diclofenac.]
- Questioned whether there was any evidence that would suggest that a more restrictive schedule should apply to dermal diclofenac products containing up to XXXXX per cent diclofenac.

- Reiterated that dermal preparations containing 1 per cent diclofenac had been marketed for many years in Australia and internationally with well demonstrated quality, efficacy and safety.
- Also reiterated that the XXXXX per cent spray gel had been marketed in the UK and other European countries, and there had been no emerging issues that would suggest that dermal preparations up to and including 4 per cent diclofenac would not demonstrate the same safety and efficacy profile.
- In relation to the comment on lack of results of a microdialysis study, contended that such study would not provide essential information on the safety and efficacy of the XXXXX per cent gel. The systemic plasma levels of XXXXX per cent gel administered twice a day were comparable to the 1.16 per cent product applied four times per day, therefore a similar systemic safety profile could be expected. Asserted that the skin safety of the XXXXX per cent gel product was confirmed in clinical trials.
- In relation to the comment that the XXXXX per cent product was not yet registered anywhere in the world, stated that since submitting the application, approval of XXXXX per cent gel has been granted OTC status in Portugal and Finland.
- Stated that the XXXXX per cent spray gel has now been registered in 18 European countries, as well as in New Zealand.
- In relation to the overdose risks with topical preparations, the evaluator argued that the information considered adequate to cover this matter was not provided in the application. The applicant responded that this safety information was included in the applications for registration to be evaluated by the TGA.
- Acknowledged that the evaluator agreed that the product should not be used in pregnancy (including the third trimester because of a possible effect on the ductus arteriosus).
- Concluded that the scheduling of all dermal preparations above 1 per cent and not more than 4 per cent diclofenac as Schedule 2 preparations for the short-term (7-21 days) treatment of pain and inflammation, provided consumers with appropriate choices for the treatment of their musculoskeletal conditions.

October 2011 Pre-meeting Submissions

Two submissions were received. XXXXX did not support the exemption from scheduling for dermal diclofenac. The main points of these submissions are summarised below:

XXXXX

Proposed a scheduling cascade of a Schedule 4 entry for dermal preparations containing 3 per cent or more of diclofenac, irrespective of indications for use, and Schedule 3 or Schedule 2 for dermal preparations containing more than 1 per cent and less than 3 per

cent of diclofenac, irrespective of indications for use. The proposals were based on the following:

- Explained that the cut-off limit in Schedule 4 of 3 per cent reflected the currently available concentration of diclofenac in dermal product for the management of solar keratosis.
- Stated that topical diclofenac was a useful and relatively safe treatment for pain and inflammation when used appropriately. Highlighted, however, that diclofenac and other commonly available NSAIDs have been associated with increased CV risks. Stated that even with the use of topical preparations, these risks were increased with:
  - Stronger products.
  - Inappropriate use such as more frequent application or application to larger areas.
  - Concomitant use with oral NSAIDs or aspirin.
- Stated that stronger products should be included in Schedule 4, providing clarity to pharmacists and prescribers. For moderate strength, topical diclofenac products could be available without prescription with access to advice from a pharmacist.
- Proposed a Schedule 3 etnry for topical preparations containing more than 1 per cent and less than 3 per cent diclofenac, on the condition there was a commitment from sponsors to support pharmacy assistant training.

The submission also addressed a number of criteria under section 52E, as summarised below:

(a) Risks and Benefits

- All NSAIDs have a similar capacity to cause renal impairment, congestive heart failure, hypertension and oedema.
- Chronic sustained systemic exposure to NSAIDs, particularly in patients over 65 years of age was of concern owing to documented increased risk of GI and CV events.
- Ibuprofen was associated with the highest risk of stroke, followed by diclofenac. Diclofenac was also associated with the highest risk of CV death.
- While evidence based reviews showed 1 per cent topical diclofenac to be an effective and well-tolerated treatment in painful and inflammatory conditions for short-term use, further research was recommended.
- There was systemic exposure to diclofenac following normal use of 1 per cent diclofenac gel, up to 6 per cent of the systemic levels of a single oral dose of diclofenac sodium. Concomitant administration of diclofenac gel with oral NSAIDs or aspirin may result in increased adverse NSAID effects.

- Stronger topical preparations would cause greater systemic exposure, even with proper use. Inappropriate use such as greater frequency or larger areas of application risk even greater systemic exposure.
- With the unrestricted availability of aspirin and ibuprofen, there was a potential for people to combine these with topical diclofenac use, increasing the risk of systemic adverse effects. The elderly would be particularly at risk and considering the incidence of osteoarthritis in this age group, there was a strong likelihood that they may use topical NSAID preparations as well as oral NSAIDs; particularly with targeted marketing campaigns.

(b) Purposes for which a substance is to be used

- Stated that the recommended dosage for 1 per cent topical diclofenac for anti-inflammatory use was:
  - 2 g per joint per application for upper extremities (hand, elbow, wrist), with a maximum of 4 applications (8 g) per joint per day.
  - 4 g per joint per joint per application for lower extremities (foot, ankle, knee), with a maximum of 4 applications (16 g) per joint per day.
  - A total maximum of 32 g of gel per day.
- Claimed that considering this dosage, it was assumed that a XXXXX per cent gel would equate to a total maximum of 16 g of gel per day and a XXXXX per cent spray gel would equate to a total maximum use of 8 g per day. Stated that considering the risks described earlier, it would be essential for consumers to be supported in the appropriate use of stronger preparations.
- Suggested that access to stronger products could be through discussion with a pharmacist as a Schedule 3 medicine. Also suggested that with appropriate training of pharmacy assistants, stronger products could be included in Schedule 2 to facilitate referral to a pharmacist as appropriate.

(c) Dosage, Formulation, Labelling, Packaging and Presentation

- Stated that restrictions to different strengths of a medicine under one schedule could be confusing for pharmacists. Mentioned that under the applicant's proposal, diclofenac for dermal use could be listed as Schedule 4 if:
  - in preparations containing more than 4 per cent diclofenac when not indicated for solar keratosis; or
  - in preparations indicated for solar keratosis.
- Raised concerns that pharmacists may be confused as to when they can or cannot supply stronger topical diclofenac preparations without a prescription. Concerned with Schedule 4 diclofenac 3 per cent (for solar keratosis) products being supplied without a prescription as an anti-inflammatory.

- Argued that this was an issue with mometasone nasal spray, which is included in Schedule 2 for the treatment of allergic rhinitis in adults and children 12 years of age and over. However, the only available product on the market was a Schedule 4 product. Stated that pharmacists regularly enquire if this product can be supplied without a prescription. Explained that its advice had been that as the product did not meet the labelling and packaging requirements for a Schedule 2 medicine, it should not be supplied as such without advice from jurisdictional pharmacy services. Stated that feedback from pharmacists indicated that advice from jurisdictional pharmacy services had not necessarily clarified the matter and pharmacists remain confused on this issue.
- Concerned that the proposed listing for diclofenac could cause similar confusion. Irrespective of whether diclofenac 3 per cent was indicated for solar keratosis, as a 3 per cent topical product it remains Schedule 4.
- Suggested that limiting the Schedule 4 entry by strength rather than indication would provide greater clarity.
- Raised concerns that product labelling of preparations containing 2 per cent or less, or 4 per cent or less diclofenac, would not adequately ameliorate safety risks.
- Also raised concerns that topical diclofenac products may be inadvertently misused by people who do not understand the directions or the precautions. There would be a risk of administration to children or the elderly, or use for extended periods or in combination with other NSAIDs (including oral dosage forms) without consulting a health professional.
- Claimed that in the interest of public safety, it was essential that support was aimed at the lowest common denominator, and relying solely on having information on a medicine pack was not appropriate if there is any risk of misuse.

(d) Other Matters

- Stated that a recent program (Pharmacy Guild of Australia's Standards Maintenance Assessment) had revealed that almost all consumers had received some advice from pharmacy personnel with the purchase of Schedule 2 or Schedule 3 medicines.
- Argued that it would be expected that there would be no information gathering or provision of professional advice associated with medicines supplied through the grocery sector.
- Asserted that pharmacy assistants must complete appropriate training regarding Schedule 2 and Schedule 3 medicines.

XXXXX

Did not support the exemption of topical preparations of diclofenac of all strengths (excluding treatments for solar keratosis) and did not propose an alternative scheduling entry. The following comments were made:

- Noted that the two "alternative approaches" in the public notice offered the possibility of retaining an upper limit (up to 4 per cent) to the concentration for exemption from scheduling.
- Noted that in addition to the possibility of XXXXX per cent diclofenac preparations being exempted from scheduling, the proposal could also result in an expanded range of products being exempted as it refers to "topical" (rather than "dermal") preparations. [Members noted that they had no intention of broadening any scheduling entry beyond the current dermal use wording.]

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that 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 safety, and (d) the dosage; formulation and presentation of a substance.

Members, after discussing the matters set out below, agreed to the evaluator's recommendation to reschedule diclofenac when in dermal preparations containing more than 1 per cent up to, and including, 4 per cent of diclofenac from Schedule 4 to Schedule 2.

Members discussed whether there was justification for loosening the current Schedule 4 classification for dermal preparations containing more than 1 per cent diclofenac. There was general agreement that 1 per cent or less dermal preparations should remain exempt.

OTC vs. Schedule 4

Members first discussed the systemic bioavailability of diclofenac in dermal preparations. A Member noted that diclofenac administered dermally penetrates slowly and in small quantities compared with equivalent oral administration. Another Member noted that despite a lower systemic bioavailability diclofenac concentrations in the target tissue were higher than achieved through oral administration of diclofenac.

Members noted the risks of concurrent use of dermal NSAIDs with anticoagulants, which has been associated with severe or fatal haemorrhage. A Member stated, and the Committee generally agreed, that since systemic absorption of diclofenac from dermal applications was lower than oral administration, such interactions were unlikely to occur.

A Member, noting the extent of use overseas for these higher strength diclofenac dermal preparations, limited AEs and reasonable dermal tolerability, argued that such preparations should be available OTC. Several Members, however, were unconvinced that there was a need for such preparations OTC. The following was discussed:

- A Member stated that there has been no clinical evidence supporting a superior efficacy of dermal formulations containing more than 1 per cent diclofenac vs. 1 per cent preparations. The Member asserted that unless there was a measurable efficacy and safety profile, a Schedule 2 entry would not be appropriate. The Member was

concerned that higher strength dermal preparations would therefore be promoted as a marketing tool rather than because of a need.

- A Member noted that the application's primary justification for needing a higher strength formulation was a claim that it would be more convenient, requiring less frequent application.
- Members noted that AE reports showed a higher number of AEs for 3 per cent than for XXXXX per cent dermal preparations. A Member stated, however, that the safety data showed that the AE profile of XXXXX per cent gel and XXXXX per cent spray gel preparations were similar to those observed in 1.16 per cent diclofenac gel preparations. A Member highlighted that this similarity could be due to less skin irritation AE with XXXXX per cent spray gel which requires fewer applications than preparations containing lower concentration of diclofenac. In addition the affected area does not need to be touched when using spray gel formulation.
- A Member stated that formulation affects the efficacy of diclofenac, including solvent and excipients, and cited an example of DMSO used in diclofenac formulations, which was a concern. The Member argued that without further data, the down scheduling from Schedule 4 should not be supported. However, another Member stated that such matters for new diclofenac dermal products should be left to the TGA's evaluation and registration process.

Members generally agreed that it was appropriate for these higher strength dermal diclofenac preparations to move from Schedule 4 to an OTC schedule.

Schedule 3 vs. Schedule 2

Members then discussed whether these higher strength dermal diclofenac preparations should be Schedule 2 or Schedule 3. Points discussed included:

- A Member remained reluctant to allow these preparations to be included in Schedule 2 due to a lack of efficacy and safety data. Another Member argued that there has been enough safety data on diclofenac dermal preparations available overseas to support a Schedule 2 entry.
- A Member asserted that higher strength diclofenac dermal products could be Schedule 2, as long as there was access to professional advice. Another Member contended that if professional supervision was deemed necessary then it should be included in Schedule 3.
- A Member contended that if formulations were to be compared, then these higher strength dermal preparations should be in Schedule 2 as consumers would actually get a lower dosage of diclofenac from the dermal preparations than those divided oral preparations currently in Schedule 2.
- Members noted that the applicant welcomed the evaluator's recommendation to have 1 to 4 per cent diclofenac listed in Schedule 2.

- Members also noted that in the UK all diclofenac dermal products were classified as Pharmacist medicines, while market approval for a 2 per cent gel product was granted in Portugal, and a 4 per cent spray gel had been granted approval in 15 countries.

Members generally agreed that dermal preparations containing more than 1 per cent, up to and including 4 per cent should be Schedule 2 rather than Schedule 3.

Solar keratosis

Members then discussed whether there was any reason to amend the current Schedule 4 status of dermal diclofenac preparations when intended to solar keratosis treatment. The following was discussed:

- A Member discussed a pre-meeting submission's proposal to include dermal preparations containing 3 per cent of more diclofenac in Schedule 4 without any reference to solar keratosis. A Member stated that this approach could assist pharmacists by limiting confusion at the point of supply. Members noted, however, that there were a number of substances which had different scheduling for different indications (e.g. certain products used for the treatment of tinea pedis were available unscheduled while also being available as Schedule 2 for other dermal uses and Schedule 4 for formulations other than dermal).
- A Member asserted that it was unlikely that different concentrations of diclofenac in dermal preparations available OTC and prescription would lead to consumers' confusion.
- The subject of off-label use of OTC dermal preparations for solar keratosis was noted by the Members. A Member argued that if high concentrations of dermal diclofenac were available OTC, patients with solar keratosis could obtain these products from pharmacy shelves without access to professional advice. Members recognised that it would be difficult to mitigate off-label use for solar keratosis but did note that there would be a price incentive with the non-solar keratosis product expected to be more expensive.

Members agreed that preparations for solar keratosis should remain Schedule 4, regardless of diclofenac concentration.

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 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 safety, and (d) the dosage; formulation and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to reschedule dermal preparations containing more than 1 per cent up to 4 per cent or less of diclofenafc, except when for the treatment of solar keratosis, to Schedule 2. The delegate also decided that Schedule 4 remains appropriate for preparations containing more than 4 per cent of diclofenac. The delegate confirmed that preparations containing 1 per cent or less of diclofenac would remain unscheduled and that preparations for use in solar keratosis would remain Schedule 4. The delegate also decided that an implementation date of 1 May 2012 was appropriate (i.e. three months following the delegate's final decision).

Schedule 2 – Amendment

DICLOFENAC – Amend entry to read:

DICLOFENAC when:

(a) in divided preparations for oral use containing 12.5 mg or less of diclofenac per dosage unit in a pack containing 20 or less dosage units and labelled with a recommended daily dose of 75 mg or less of diclofenac; or

(b) in preparations for dermal use containing 4 per cent or less of diclofenac **except** in preparations for dermal use containing 1 per cent or less of diclofenac or for the treatment of solar keratosis.

Schedule 4 – Amendment

DICLOFENAC – Amend entry to read:

DICLOFENAC **except**:

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

(b) in preparations for dermal use unless:

(i) for the treatment of solar keratosis; or

(ii) containing more than 4 per cent of diclofenac.

2.2.3 FAMCICLOVIR

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Famciclovir – Seeking advice on a proposal to reschedule 1500 mg or less of famciclovir from Schedule 4 to Schedule 3 when in oral preparations for the single dose treatment of herpes labialis (cold sores) in immunocompetent patients.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended the down scheduling of famciclovir for oral use, in divided preparations containing a total dose of 1500 mg or less of famciclovir for the treatment of herpes labialis (cold sores) from Schedule 4 to Schedule 3.

The Committee also agreed to an implementation period of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Famciclovir is a synthetic guanine derivative. It is the oral form of penciclovir. Famciclovir is rapidly converted *in vivo* into penciclovir, which has *in vitro* activity against herpes simplex viruses (HSV types 1 and 2) and varicella zoster virus. *In vitro* studies demonstrated that in infected cells, the viral thymidine kinase phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. Penciclovir triphosphate inhibits HSV-2 DNA polymearase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited. Penciclovir triphosphate persists in infected cells in excess of 12 hours. The long intracellular half-life of penciclovir triphosphate ensures prolonged antiviral activity.

In June 1994, ADEC (now the Advisory Committee of Prescription Medicines or ACPM) recommended approval for the registration of famciclovir for the treatment of herpes zoster infection. In May 1995, the NDPSC agreed to include famciclovir in Schedule 4.

The TGA approved famciclovir for the treatment of recurrent herpes labialis in January 2007. The approved dosage was 1500 mg administered either as a single dose or 750 mg twice daily at 12 hourly intervals (to a total dose of 1500 mg per episode).

Famciclovir was also TGA-registered for the treatment of recurrent episodes of genital herpes in adults and adolescents 12 years of age and older, and for the suppression of recurrent genital herpes. Famciclovir was also indicated for immunocompromised patients with uncomplicated herpes zoster, recurrent herpes simplex and/or recurrent herpes simplex.

In November 2001, the NDPSC agreed to exempt preparations containing 5 per cent or less of aciclovir for the treatment of herpes labialis in packs containing 10 g or less, on the grounds that herpes labialis was a short-term and self-limiting condition, appropriate

for self-diagnosis and management by consumers. In addition, the product was simple to use and increased access to such a product would be beneficial to public health.

In February 2009, the NDPSC considered a submission to down-schedule famciclovir (single oral dose) for the treatment of herpes labialis in immunocompetent patients from Schedule 4 to Schedule 3 and inclusion in Appendix H. The NDPSC noted the potential risk of generating resistance in the community and thus putting immunocompetent patients at risk. The NDPSC also noted that in immunocompetent patients, the condition was self-resolving and the benefit of oral treatment over topical therapy was not significant. Overall, the NDPSC was of the opinion that the risks associated with down-scheduling outweighed the benefits, and given that, the NDPSC agreed that the current scheduling remained appropriate.

The same rescheduling proposal was considered at the October 2009 NDPSC meeting. The applicant provided additional data that showed absence of evidence of resistance developed by immunocompromised patients. The application also provided a draft pharmacist treatment algorithm and discussed some educational initiatives. The NDPSC noted that a lack of evidence of resistance was not the same as evidence proving that over-the-counter (OTC) use of famciclovir orally would not lead to resistance. The NDPSC decided that the current Schedule 4 remained appropriate.

In May 2009, the New Zealand Medicines Classification Committee (MCC) meeting rejected a submission for the reclassification of famciclovir 500 mg tablets from prescription medicine to restricted medicine in packs of three tablets for the treatment of recurrent herpes labialis. Subsequently, at its November 2009 meeting, the MCC reconsidered the submission with further information on warnings and training material relating to use in immunocompromised patients. The MCC agreed to reclassify famciclovir 500 mg tablets to restricted medicine.

In February 2010, the NDPSC considered whether to harmonise with the MCC's November 2009 decision in reclassifying famciclovir to restricted medicine. The NDPSC contended that the MCC's decision to reclassify famciclovir was dependant on a number of NZ specific requirements (including development of an appropriate treatment algorithm), and argued that Australian jurisdictions may not be able to enforce these requirements to a similar degree. The NDPSC decided not to harmonise with NZ.

XXXXX submitted an application to the Secretariat in support of the rescheduling of famciclovir. A delegate agreed that this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

SCHEDULING STATUS

In Australia, famciclovir is scheduled in Schedule 4. In NZ, famciclovir is classified as prescription or restricted (equivalent to Schedule 3) when in tablets containing 500 mg or less of famciclovir when sold in a pack approved by Medsafe.

INITIAL SUBMISSIONS

Applicant's submission

XXXXX requested the rescheduling of famciclovir from Schedule 4 to Schedule 3 for 1500 mg in a single oral dose for treatment of herpes labialis in immunocompetent patients. XXXXX was not seeking inclusion in Appendix H.

[Members noted that the single 1500 mg oral dose treatment does not refer to a single tablet, it refers to multiple 500 mg tablets taken at the same time to give the 1500 mg dose.]

The applicant stated the following:

- That it submitted the same rescheduling proposal and a request for inclusion of famciclovir in Appendix H on two previous occasions to the NDPSC (February 2009 and October 2009).
- That essential aspects of this resubmission cover the main concerns of the two previous considerations.
- That the major points of the application again covered the following matters:
  - Potential of viral resistance with use of famciclovir, particularly within immunocompromised patients.
  - Efficacy and benefits of a single dose of famciclovir compared with existing multi-use topical treatments.
  - Appropriateness of use of single dose famciclovir for treatment of recurrent herpes labialis in immunocompetent patients compared with multi-day famciclovir.

The applicant maintained the position that single oral dose famciclovir was appropriate to be classified as a Schedule 3 medication. A summary of the application is outlined below:

- Asserted that overall, single-dose oral famciclovir for the treatment of recurrent herpes labialis in immunocompetent patients had a good risk-benefit ratio and was a treatment appropriate for classification as a Schedule 3 entry.
- Also asserted that a single dose of 1500 mg famciclovir had an acceptable safety profile and pharmacist intervention, supported by a proposed treatment algorithm and protocol, would minimise the risk of off label use.
- Stated that at the February 2010 NDPSC meeting, a Committee member commented that the risk *vs.* benefit profile of famciclovir was similar to that of aciclovir which was unscheduled for the treatment of herpes labialis, and this was not refuted by the Committee.

- The product was restricted in use to patients 18 years of age and over, primarily due to nominal restrictions in the patient inclusion criteria in the pivotal trial.
- The use of famciclovir was not expected to produce dependency. Oral famciclovir has been marketed globally for 18 years and there had been no reported cases of abuse in clinical practice. The pharmacist, with the assistance of the proposed treatment algorithm and protocol was well placed to screen for patients for whom the product was not recommended e.g. immunocompromised patients.
- Asserted that there was little potential for harm if used incorrectly by immunocompetent patients without cold sores or outside the prodromal period. Due to the product presentation being limited to a single dose of 1500 mg famciclovir, this would further limit the potential for any misuse.
- Famciclovir had been well tolerated in human clinical studies and the risk factors for adverse effects were identifiable and manageable by a pharmacist. There were no known contraindications apart from hypersensitivity to famciclovir (or penciclovir) and no clinically significant interactions had been identified.
- Famciclovir was intended for treatment of a condition which was acute, recurrent, self limiting and appropriate for self diagnosis by consumers who could readily recognise the onset of symptoms and lesions. The condition did not require medical diagnosis or close medical management, unless in immunocompromised or renally impaired patients, for which famciclovir was not recommended.
- When considering masking of a serious disease or compromising medical management the only issue was the misuse of the product in immunocompromised patients, for whom a longer dosing regimen was required; or renally impaired patients. This was addressed with provision of the algorithm and treatment protocol designed for pharmacists to help screen patients.

The applicant made the following statements on the public health impact of a Schedule 3 entry:

- Eighteen per cent of all adults aged 18 or older suffer from herpes labialis at least every 2 years. Cold sores develop most commonly on or adjacent to the lips and last a mean of about 5-6 days although this could be variable up to 20 days.
- Early treatment of cold sores was cosmetically desirable and clinically most effective because viral replication was most active in the prodromal period or within the first 8 hours after lesion onset. Asserted that an ability to self-medicate with a single dose within the first few hours of the onset of the prodromal symptoms would be beneficial.
- The single oral dose treats all lesion sites while topical therapies would only treat primary lesions at the site of application.
- Patient compliance would improve because of the convenience of taking a single oral dose rather than applying a topical treatment up to 5 times a day for four days. This

makes single dose oral famciclovir a unique and arguably more effective treatment option to the conventional OTC topical cold sore preparations available.

- Where use of an oral treatment is preferred, the removal of the need for a patient to firstly consult a medical practitioner and obtain a prescription is likely to lead to earlier and therefore more effective treatment with a reduced period of infectivity. This would also relieve pressure on the service demands on GP Clinics.
- Access to GPs was restricted in some communities and with the desirability of treating the cold sore within 8 hours of the first symptoms appearing, a Schedule 3 listing would reduce infection and improve treatment compliance.
- This could reasonably be expected to reduce the risk of transmission of HSV 1 within the community. Noted that Schedule 3 availability would still require the involvement of a health care professional.

The applicant provided a background which covered the following matters:

International Registration and Scheduling Status

- Stated that famciclovir was approved for the treatment of herpes labialis in the US, UK and NZ. Also stated that famciclovir was available as a prescription medicine in the US, UK and other EU countries, and XXXXX
- XXXXX

Description and Pharmacology

- The applicant provided the Product Information (PI) and a description on how the herpes viral replication are selectively inhibited.

The applicant addressed criteria against section 52E, and information not already discussed is summarised below:

(f) Risks and benefits

- In response to the NDPSC's previous concerns on the benefit of oral famciclovir over topical treatments as the condition was self resolving in immunocompetent patients, the applicant reiterated its position that single dose oral famciclovir was superior to multi-use topical therapies.
- Stated that the literature supported faster healing times with oral famciclovir treatment compared with multi-use topical antiviral therapies.
- Asserted that although it was acknowledged that there had been no direct head-to-head clinical trials for oral famciclovir versus a topical anti-viral therapy, it was reasonable to conclude that based on the evidence available, a single dose oral famciclovir demonstrated faster healing of lesions compared with topical therapies.
- Noted from the February 2010 NDPSC consideration that several Members disagreed with the argument that efficacy over existing treatments was not a requirement for

down-scheduling and asserted that during the regulatory evaluation process, famciclovir single dose preparations were found to be safe and efficacious.

- Argued that single dose oral famciclovir was more efficacious than many existing multi-use topical treatments, and that there was no evidence to suggest that it was less efficacious than existing topical treatments.
- Also stated that such benefit had already been accepted by the NDPSC in its consideration of a single dose of oral fluconazole for the treatment of vaginal candidiasis from Schedule 4 to Schedule 3. In approving the fluconazole rescheduling application in 2009, the NDPSC acknowledged that this may enhance patient compliance, i.e. single dose oral treatment compared with 3-7 successive days of topical treatment.
- Noted that the evaluation report on famciclovir prior to the October 2009 NDPSC meeting agreed that the rescheduling of fluconazole was comparable to the issue of oral famciclovir versus topical anti-viral treatment availability. [Members noted that XXXXX, was the famciclovir evaluator for the October 2009 meeting. The current evaluation was conducted by a different evaluator.]

Benefits

- Stated that famciclovir (single dose) was not recommended for use in immunocompromised patients. Asserted that the currently available Schedule 4 famciclovir was only approved for use in herpes labialis, as a single dose. Multi-day doses of famciclovir were prescribed only for genital herpes or shingles.
- Raised the possibility that some Members may have previously confused the dosage regimen for the treatment to herpes labialis with the different regimen required for shingles or genital herpes.
- Pharmacist intervention would be required to provide famciclovir (single dose), thus ensuring that the patient would be taking the product for herpes labialis. The pharmacist's professional skills would be supported by labelling and provision of the treatment protocol and algorithm to help minimise any potential misuse.
- Asserted that it would not be financially sensible for a patient to purchase a single dose of famciclovir to treat genital herpes or shingles as dosing over several days was required. If this was to occur the patient would be likely to experience a lack of efficacy, however any harm would be unlikely as described under (e) Potential for Misuse or Abuse.
- As highlighted below, there was no approved indication for multi-day treatment of famciclovir for herpes labialis.

Viral resistance

- Emphasised that the proposal to reschedule famciclovir to Schedule 3 only applied to immunocompetent patients; immunocompromised patients would be excluded from

treatment by pharmacist-screening according to the labelling, the proposed treatment protocol and the proposed treatment algorithm, which was currently in use in NZ.

- Reiterated the decision made by NDPSC to reschedule fluconazole to Schedule 3 where the risk of resistance was similar to famciclovir. Asserted that in its deliberations, the NDPSC noted the potential for resistance to be developed with fluconazole and the risk of drug-to-drug interaction. It was acknowledged that although there may be a potential for resistance to develop with long-term chronic exposure to fluconazole, this risk was unlikely to occur with administration of a single oral dose and given the episodic nature of the condition.
- Asserted that it provided published data which support the contention that antiviral drug resistance is unlikely given the single dose approach in immunocompetent patients.
- Stated that it had provided in the past published data reporting no increase in the development of viral resistance over the past 20 years despite widespread use of many antiviral preparations for various kinds of herpes infections.
- Claimed that such evidence was accepted by the TGA at the time of registration of famciclovir for the treatment of recurrent herpes labialis.
- Stated that the evaluator for the past application (February 2009) was in the opinion that the possible development of resistance was addressed in the application, in which no resistance has developed over the past 20 years, despite the widespread use of antivirals for herpes infections of various kinds. [Member noted that XXXXX was the evaluator for famciclovir for the February 2009 NDPSC consideration].
- Argued that as a pro-drug of aciclovir, the propensity for resistance with use of famciclovir was unlikely.
- Provided details of why the likelihood of viral resistance to famciclovir occurring in HSV was slow. In brief, this large DNA virus has a low mutation rate in comparison with RNA viruses. The mechanism of action and high potency of famciclovir against the virus also help to explain the low potential for viral resistance.
- Highlighted that cross-resistance of famciclovir to other antivirals had not been a problem. The most common form of resistance encountered with aciclovir and penciclovir among herpes simplex virus strains was a deficiency in the production of thymidine kinase. However penciclovir has been shown to be active against a clinically isolate aciclovir resistant HSV-1 strain with an altered DNA polymerase.
- Claimed that there had not been an emergent resistant strain which was either transmissible or detectable in, for example, genital herpes suppressive therapy (where patients forget to take their medication, which was not possible with single dose therapy), genital herpes episodes (5 day therapy with low dose aciclovir and penciclovir), herpes labialis using oral creams (low dose multiple applications) and use in HIV-positive patients in Africa (low dose aciclovir where medication was not always taken as directed).

- Highlighted a recently published paper that provided further support that famciclovir was unlikely to cause viral resistance and that the key factors in the development of antiviral drug resistance are the prolonged antiviral drug exposure and ongoing viral replication due to immunosuppression.
- Asserted that the proposed labelling directs the patient not to use famciclovir (single-dose) if they have a problem with their immune system.
- Stated that the famciclovir Product Safety Update Report (PSUR) 4 showed that no HSV resistance was detected in a randomized, multicenter, double-blind study XXXXX single-day treatment (1000 mg twice a day) with famciclovir versus placebo, in patient-initiated episodic treatment of recurrent genital herpes in immunocompetent African descendent patients.
- Claimed that drug-resistant HSV from immunocompetent patients has remained at a rate of 0.1 - 0.7 per cent of isolates. Drug-resistant HSV is more commonly isolated from immunocompromised patients and occurs at a rate of 4 - 7 per cent of isolates although the prevalence among these patients has also remained stable.
- Stated that using chronic suppressive treatment with penciclovir or famciclovir in immunocompetent and immunocompromised patients in 11 global clinical trials, there was no evidence of reduced penciclovir sensitivity in viral isolates obtained during or after treatment.
- Stated that the results from studies of up to four months' treatment with famciclovir, showed that no resistance occurred as a result of treatment with either famciclovir or penciclovir.
- Concluded that given that the application was for a single dose treatment and not for continuous suppressive therapy, and since penciclovir is selectively activated in HSV infected cells only, viral resistance is not considered to be an issue.

Use in immunocompromised patients and renally impaired patients

- Reiterated that immunocompromised patients were not eligible for OTC treatment with single-dose famciclovir due to the potential for a more severe and prolonged disease, and the need for these patients to receive special and individualised treatment.
- Assured that the treatment algorithm used in NZ included a question intended to assist the pharmacist to identify consumers who may be immunocompromised and need to be referred to a general practitioner.
- Highlighted that any patient who was a regular customer at a particular pharmacy could potentially be identified as unsuitable for self-treatment based on the pharmacist's own records and would therefore be referred to their doctor for medical advice.
- Stated that oral famciclovir was PBS listed for episodic treatment and suppressive therapy of moderate to severe herpes labialis in immunocompromised patients.

According to the Public Summary Document (PSD), a document containing information pertaining to the Pharmaceutical Benefits Advisory Committee or PBAC recommendations, relating to this listing, "The likely number of patients/year was estimated to be < 5,000 in year 4.".

- Claimed that this relatively small number of immunocompromised patients who might present for treatment, combined with the measures in place to exclude such patients from self-treatment, suggests that the overall benefit of allowing patients early access to oral famciclovir in the pharmacy setting would outweigh the small risk associated with inappropriate use in immunocompromised patients.
- Claimed that it was acknowledged that it was unrealistic for a pharmacist to dose-adjust for renally impaired patients within the pharmacy setting, therefore, patients with renal impairment were specifically excluded from self-treatment with famciclovir for herpes labialis via the treatment algorithm.
- Asserted that the screening out of renally impaired patients would also be reinforced to pharmacists via the proposed algorithm and treatment protocol.
- Also asserted that the product labelling and pack insert would alert patients to the need for medical advice if they suffered from any problems with their kidneys or have diabetes (diabetic patients are at risk of having renal impairment).
- Stated that patients with renal impairment were generally aware of their condition and were cautious of taking any medication which may not be appropriate.

(g) Purposes and the extent of use

- Single dose oral 1500 mg XXXXX is indicated for the treatment of cold sores caused by herpes simplex virus type 1 (HSV-1) infection.
- Explained that after the first (primary) infection, the virus is transported to the dorsal root ganglia, a cluster of sensory nerve cells, near the brain stem (trigeminal), face or vagus nerve and lays dormant. During latency the genome persists inside infected cells. It may manifest as herpes labialis upon reactivation following a trigger that stimulates virus replication and transport to the nerves of the skin and/or mucous membranes.
- The easy recognition of herpes labialis symptoms makes the condition appropriate for self diagnosis and management by patients.

(h) Toxicity and safety

- Stated that the information below was previously submitted for consideration at the February 2009 NDPSC meeting. Main points were reiterated below:
  - Asserted that the human toxicity profile of famciclovir was well characterised and it has been well tolerated in human clinical studies. Headache, fatigue and nausea were reported as the main side effects at a similar incidence in patients receiving placebo treatment.

- There were no known contraindications apart from hypersensitivity to famciclovir (or penciclovir) and no clinically significant interactions have been identified.
- Confusion, predominantly in the elderly, was reported rarely. Asserted that reports of serious side effects including skin reactions and thrombocytopenia were very rare in the post marketing setting and stated that close medical monitoring should not be required at the doses recommended for treating herpes labialis.
- Famciclovir has been administered in courses lasting from one day to chronic administration for suppression of recurrent disease. Stated that side effects were expected to be minimal during episodic treatment of cold sores in a single-dose regimen.
- The package insert would advise that dizziness, somnolence or confusion may arise and to avoid driving or operating machinery.
- Famciclovir interacts with commonly used medicines or food. Asserted that these interactions could be managed by a pharmacist.
- It has a medium to wide therapeutic index. It was approved for treating acute conditions at doses ranging from 125 mg twice a day to 1500 mg daily, as well as for long-term chronic use at doses up to 1000 mg daily.
- Famciclovir cold sore product pack would be presented in discrete cartons containing a total of 1500 mg of famciclovir for the treatment of a single cold sore episode only.
- Asserted that therefore, the likelihood of toxicity or overdose with the 1500 mg famciclovir pack was minimal. This was further supported by dosing of up to 2.25 g famciclovir per day in some clinical studies. The PSUR No 3 states experience with intentional or accidental overdose of up to 5.25 g famciclovir over 3 days or 3 g in one day, which have not resulted in any adverse effects.
- A report of accidental acute overdosage of 10.5 g of famciclovir was asymptomatic.

(i) Dosage, formulation, labelling, packaging and presentation

· XXXXX

· Affirmed that the proposed Schedule 3 OTC presentation would be specifically labelled for the treatment of cold sores, and that it will be appropriately packaged to ensure that the dosage regimen and duration of treatment are adhered.

· Stated that if the condition failed to improve or respond, the following statement would be printed "If your cold sore symptoms do not improve within a few days, or if they become worse, tell your pharmacist or doctor.".

· Assured that there would also be a specific CMI in the box and a revised PI would be provided. The package insert would describe contraindications, situations where

caution was needed, potential adverse reactions and provide advice on what actions to take if allergic or adverse effects were experienced.

(j) Potential for misuse / abuse

- Stated that there had been no reported cases of famciclovir abuse in clinical practice.
- Also stated that the potential for famciclovir (single dose) abuse would be equally unlikely, because the product would be presented in a pack containing XXXXX, which is sufficient for the treatment of a single episode of cold sores only, further limiting any potential for intentional abuse.
- Claimed a low potential for harm from inappropriate use as there was considerable clinical and post-marketing experience in immunocompetent and immunocompromised patients with high doses of famciclovir as well as chronic therapy with famciclovir.
- Stated that there was little potential for harm if used incorrectly by immunocompetent patients without cold sores or outside the prodromal period.
- Also stated that the use of famciclovir to treat cold sores was limited to patients over 18 years of age primarily due to nominal restrictions in the patient inclusion criteria in the pivotal trial.
- Claimed that while there was no intention to reduce the age limit, it should be noted that the current Schedule 4 product was also approved for use in children as young as 12 years old in other indications.
- Asserted that there have been no cases of serious adverse effects reported in children. Also, the proposal to reschedule this pack to Schedule 3 should not increase the risk that children younger than 12 years might inadvertently take the product while at home.
- Stated that the product maintained the same risk as associated with any similar presentation of a prescription medicine and would be mitigated by the label warning 'to keep the product out of the reach of children'.
- Reiterated that famciclovir was indicated for treatment of cold sores in immunocompetent adults. Adult immunocompromised patients with recurrent HSV infections including orofacial lesions require a different famciclovir dose taken over a number of days (500 mg twice a day for 7 days for episodic therapy; 500 mg twice a day for suppressive therapy).
- Asserted that the treatment algorithm also highlighted the need to exclude particular consumers (e.g. elderly, pregnant or breastfeeding patients, and the renally or hepatically impaired) and to refer others to their physician.
- Recognised that there was a potential risk of some consumers to use it for recurrent genital herpes (RGH). Explained that this risk was considered minimal given: the requirement for intervention by the pharmacist at the point of sale; and the price

differential of an OTC cold sores 3 tablet pack versus the quantities available on PBS prescription. Asserted that the pack size and presentation of the product did not facilitate the correct dosing regimen required for RGH, providing further disincentive to intentional inappropriate use.

- Highlighted that the evaluation report presented at the February 2009 NDPSC meeting agreed that there was 'low potential for harm from inappropriate use given the pack size and the considerable experience of famciclovir use in children aged between 12 and 17 years.'.
- Also highlighted that the evaluation report presented at the October 2009 NDPSC meeting stated that "There have been no emerging safety concerns with Schedule 4 famciclovir usage".

Evaluation Report

The evaluator supported the down scheduling to Schedule 3. The evaluator recommended that the applicant undertake further work on dosage adjustment in renal failure patients to further support the rescheduling to Schedule 3. The following specific recommendations were made for the applicant:

- Obtain advice from a specialist in renal medicine with a view to improving the questions that a pharmacist should ask about possible renal impairment, and with a view to a modification of the algorithm used in NZ.
- The reason for the above was based on the ability of pharmacists to identify patients with impaired renal function and to recommend appropriate dosage adjustment or (as in NZ) referral to a doctor.
- Provide data about the effect of various degrees of renal failure on the pharmacokinetic (PK) parameters of a single dose and the consequences to human organs and for adverse events (AEs) of high plasma concentrations of penciclovir following a single dose.

In the evaluator's opinion, apart from the above, there was no other impediments to the rescheduling of single doses of famciclovir, with a total dose of 1500 mg or less, for the treatment of herpes labialis in immunocompetent subjects to Schedule 3, for the following reasons:

- Single dose oral therapy was no less efficacious and probably more efficacious than multi-day topical treatments.
- Single dose oral therapy confered a considerable advantage over topical treatments in terms of likely compliance with dosage instructions.
- There was no registered "multi-dose" therapy for herpes labialis.
- There was substantial updated evidence that resistance to antiviral treatment of HSV was rare. Concern about antiviral resistance was not a reason to preclude wider use of single dose famciclovir therapy for herpes labialis.

- Supply by pharmacists for off-label use by immunocompromised subjects seemed highly unlikely.

The evaluator also assessed the applicant's statements addressing previous NDPSC concerns, as summarised below:

Benefit of oral treatment over OTC topical therapy

- Highlighted that a reason previously raised by the NDPSC for rejecting a down scheduling was that the benefit of oral treatment over topical therapy was not significant.
- Contented that this matter would not have arisen if the applicant was able to provide results of a blinded randomised clinical study comparing oral therapy with topical therapy. Stated that the applicant acknowledged that no such head-to-head study had been conducted. Also stated that the applicant summarized results of several separate studies and acknowledged that the comparisons involve between-trial comparisons.
- Argued that the application mentioned a report on improvement in lesion healing time of topical treatment (+hydrocortisone) *vs.* placebo, however, the figure of 0.7 day improvement could not be found in the report.
- Agreed that there was no evidence to suggest that single dose oral famciclovir was less efficacious than existing topical treatments.

Single oral vs. multi day oral

- Stated that it would be helpful for the applicant to provide data on famciclovir for treatment of herpes labialis of single dose or twice daily dose for one day compared with multi-day dosing.
- Mentioned that the PI for for valaciclovir described two studies in subjects with a history of recurrent herpes labialis, which showed that a 2-day regimen did not offer additional benefit over the 1-day regimen.

Risk of viral resistance

- Recalled the NDPSC's previous concerns that the risk of generating resistance in the community and putting immunocompetent patients at risk did not reflect a good risk benefit ratio.
- Stated that the development of resistance to antiviral treatment by HSV continued to be described as rare. Also stated that the application included two review articles which deal with development of resistance by various viruses.

Risk in immunocompetent patients

- In the evaluator's opinion, the greatest deficiency in the application, both with respect to information and the algorithm, was in the context of use by patients with renal

failure. Added that in the context of community use for treatment of herpes simplex, chronic kidney disease (CKD) was of concern (patients with acute renal failure will generally be hospitalised). In addition, patients with CKD were at high risk of death from cardiovascular disease. The evaluator provided extracts about CKD.

- Stated that there was no suite of medicines that was definitive for a particular degree of renal impairment. Raised concerns of whether pharmacists could appropriately recommend dose adjustment.
- Highlighted that the famciclovir PI under Elderly Patients heading states: "No dose adjustment based on age is recommended unless renal function is impaired".
- Stated the risk of famciclovir use in immunocompetent patients, where the condition was self-resolving and the ability of pharmacists to recognise who was immunocompromised would be limited. Also stated that dose adjustment in patients with renal impairment would be unrealistic in a non-hospital setting.
- Believed that the NDPSC's concern on the ability of pharmacists to identify immunocompromised patients was addressed in decision point in the algorithm used in NZ: "Immunocompromised? Organ transplant recipient / radiotherapy / chemotherapy / antiretroviral therapy". Suggested however, that it would be more helpful to the pharmacist if posed questions as, viz: "Immunocompromised? Are you taking any antiretroviral medicines or medicines to prevent a transplant rejection? Have you had recent chemotherapy or radiotherapy?".
- In relation to the possibility of off label use by immunocompromised patients, the evaluator believed that given that the drug was a PBS item for episodic treatment and suppressive therapy of moderate to severe herpes labialis in immunocompromised patients, it seemed unlikely that such patients would purchase and take multiple doses of the single dose therapy in order to achieve efficacy.
- Added that the medical advice about disease manifestations and treatments would usually be given to immunosuppressed patients, and that these patients may be well briefed that the single dose therapy will not work.

Applicant's Response to the Evaluation Report

The applicant welcomed the evaluator's recommendation to modify the pharmacists' algorithm and provide data requested with regard to renal impairment. Also welcomed the evaluator's view that there were no other impediments to the rescheduling of famciclovir (single dose) to Schedule 3. It addressed the specific issues raised by the evaluator, which is summarised below:

Modification of pharmacist algorithm

- The applicant has consulted with XXXXX, a consultant physician in nephrology on how the screening questions might be improved. The consultant has recommended screening questions to include whether patient is over 50 years of age (algorithm previously stated over 60 years of age); a smoker; has diabetes; hypertension;

established cardiovascular disorder; obese; family history of chronic kidney disease or of Aboriginal or Torres Straight Islander origin. The modified treatment protocol and algorithm was provided in the response.

- Stated that on the consultant's suggestion, for patients at risk of chronic kidney disease, the algorithm recommends referring such at-risk patients to their medical practitioner to request a 'Kidney Health Check'.

Effect of renal failure on the PK parameters of a single dose

- Stated that although there were no measurements of PK data for a single dose of 1500 mg in patients with renal impairment, the available information on the PK of penciclovir in patients with varying degrees of renal insufficiency was presented.
- Provided data on AUC estimates that characterised the daily systemic exposure to penciclovir in patients with herpes zoster treated with famciclovir 500 mg three times a day (standard regimen). Stated that these estimates were used as reference exposure values for dose adjustment in patients with renal impairment.

PK in patients with varying degrees of renal impairment

- Asserted that it had been investigated in three studies, a single dose study and two studies with single and repeated dosing. Stated that the PK results obtained in these studies consistently showed that apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Stated that this was in agreement with the fact that penciclovir is predominantly eliminated unchanged by the kidney.

PK in haemodialysis patients

- Mentioned that the PK of famciclovir in haemodialysis patients had been investigated after single and repeated dosing. Claimed that despite the slow elimination of penciclovir from plasma in the periods between dialysis there was little accumulation of penciclovir following repeated 250 mg four times in 48 hours dosing compared to the 250 mg single dose. Explained that most likely this was due to the fact that the repeated doses were all given following a dialysis treatment.
- Summarised that a 250 mg dose of famciclovir given to haemodialysis patients following each dialysis treatment, i.e. every 2 or 3 days, was not expected to result in systemic exposure to penciclovir exceeding the exposure in herpes zoster patients treated with the standard 500 mg t.i.d. dosing regimen. Stated that no additional doses of famciclovir are recommended in the periods between the dialysis treatments.

Consequences to human organs

- Stated that in the preclinical studies, after repeated administration, the major target organs for toxicity were identified as the kidney and the testes.
- Also stated that in patients there were no clinically significant effects on sperm parameters following oral administration of famciclovir at 250 mg twice a day for 18 weeks.

Adverse events of very high plasma concentrations of penciclovir

- Stated that the available post-marketing data were selected regardless of the dosage and the dosage was not able to be separated out, and no AEs of very high plasma concentrations were specifically identified.
- Stated that a cumulative search in XXXXX post-marketing safety database was performed up to XXXXX to select all overdose famciclovir case reports worldwide. This indicated that XXXXX cases (including XXXXX events) could be identified in XXXXX patients exposed. The most frequently reported events included diarrhoea XXXXX nausea XXXXX and malaise XXXXX Diarrhoea and nausea were considered as listed in view of the proposed CMI. The unspecific term malaise seems likely related to other illnesses.
- Also stated that a safety analysis of two overdose cases including CV did not confirm a causal relationship between the intake of famciclovir and reported CV events. Concluded that no events were reported which would lead to a change of the established safety profile of famciclovir.
- Asserted that the above conclusion was assessed as satisfactory within the last EU renewal procedure. A full report on safety overview was provided in the applicant's response.

The following conclusion was provided:

- The PK data on healthy subjects and subjects with mild, moderate or severe renal failure has been discussed after administration of various doses of famciclovir. Taking this data into account, the proposed Patient Leaflet for famciclovir 1500 mg in recurrent herpes labialis includes a warning to consumers to inform the pharmacist if there is a problem with their kidneys.
- Based on the low risk of adverse events and the above statement in the Patient Leaflet, the applicant believed the risk of overdosing in consumers with renal impairment following famciclovir (single dose) was appropriately contained.

October 2011 Pre-meeting Submissions

Two submissions were received. XXXXX and XXXXX supported the down scheduling of famciclovir (single dose) to Schedule 3. The main points of these submissions are summarised below:

XXXXX

The following were considered as key points:

- Famciclovir for herpes labialis could be effectively managed through the pharmacy sector without the need for a prescription.
- Pharmacists were experienced in triaging patients and referring for further medical support when required. The availability of professional support materials for pharmacists would assist in maintaining and improving this competency.
- Also noted that aciclovir 5 per cent cream (unscheduled) is the standard topical therapy used to treat herpes labialis applied to the affected area five times a day at four hourly intervals for 5-7 days.

The submission also addressed criteria under section 52E, as summarised below:

(a) Risks and benefits

- Stated that studies had demonstrated that a one day 1500 mg course of famciclovir decreased the healing time for herpes labialis by about two days. Patients with ulcerative cold sore lesions treated with famciclovir reported a 29-36 per cent reduction in lesion healing time, however, distributing antiviral agents to the site of viral replication as early as possible was important.
- Also stated that the results from patient studies showed that no resistance occurred as a result of treatment with either famciclovir or penciclovir .
- Highlighted that caution was required when recommending famciclovir for people with reduced renal function. Asserted that there were many other products available without prescription for which caution exists in renal impairment.
- Argued that elimination of drugs was mostly through liver metabolism and/or kidney excretion, therefore it would be expected that a review of most products would advise caution with reduced renal and/or liver function.
- Emphasised that PI for famciclovir recommended that dose adjustment in immunocompetent people only if renal impairment was below 30 mL/min/1.73 m^2 and in immunocompromised people, no dose adjustment was necessary unless renal impairment is below 50 mL/min/1.73 m^2.
- Asserted that with the support of guidelines and training, reasonable triage by a pharmacist should negate this risk. If there was any uncertainty, pharmacists were trained and prepared to refer the patient to their doctor.

(b) Purposes and the extent of use

- Affirmed that the availability of an oral treatment in Schedule 3 would increase patient access for earlier treatment, which would be particularly useful for patients who find topical aciclovir to be ineffective.
- Asserted that in accordance with the Australia Bureau of Statistics (ABS), 12 per cent of Australians have indicated delays of more than 2 days to see a GP for urgent care and 12 per cent of people in outer regional or remote Australia visit hospital emergency departments because GP waiting times were too long.

(c) Toxicity and Safety

- There had been no clinically significant drug interactions reported with famciclovir or penciclovir.
- Famciclovir was generally well tolerated with headache being the most common reported adverse effect when used to treat herpes labialis.

(d) Dosage, formulation, labelling, packaging and presentation of a substance

- Stated that a once or twice daily dosage regimen with oral famciclovir was much easier to manage than a regimen requiring topical application five times a day.
- Stated that there was an increased risk of cross infection between the lips and other body parts (e.g. eyes) with the use of topical treatments for herpes labialis.
- Contended that although there may be a risk of off-label use, the cost of small pack sizes of a Schedule 3 product would be a disincentive.

(f)) Other matters

- Stated that it was willing to collaborate with professional bodies and the sponsor in developing guidelines and / or training and protocols for pharmacists.
- Asserted that pharmacists could assess whether patients were purchasing multiple packets (likely off-label use) or making repeat purchases too frequently (likely immune issue) and would be in a position to refer the patient to their doctor.
- Believed that limitations such as 'for immunocompetent patients' were better addressed by professional protocols, that were consistent with the registered indications of the product, than in a scheduling entry.

XXXXX

Supported the down-scheduling of famciclovir. An Appendix H entry was not supported, given the lack of local (Australian) data of famciclovir as a non-prescription medicine. The following points were made:

- Believed that it was paramount that the applicant supported the development of a protocol and relevant materials for pharmacists by the Pharmaceutical Society of

Australia. Stated that the protocol could appropriately address a range of issues, including those raised previously by stakeholders and NDPSC, for example:

- comparative efficacy between single-dose oral therapy, single-day multi-dose oral therapy, topical therapy and placebo;
- treatment must be initiated promptly for optimal effectiveness (and therefore appropriate access through the Schedule 3 pathway could provide benefits);
- appropriate screening processes (e.g. impaired renal function);
- prevention of off-label use through appropriate screening and referral processes;
- suggested frequency of use (e.g. for repeated requests); and
- likelihood or otherwise of the development of resistance through increased use in the community.

Previous considerations

Members noted a number of relevant points from the October 2009 NDPSC, November 2009 NZ MCC and February 2010 NDPSC meetings, which are summarised below:

October 2009 NDPSC meeting

Although the evaluator supported the application for down-scheduling, the NDPSC confirmed the current scheduling of famciclovir as Schedule 4. Reasons for this decision included:

· There was insufficient evidence of the efficacy of single oral dose vs. multi-day oral dose for herpes labialis in immunocompromised patients and Members stated it would be unrealistic to expect a pharmacist to dose-adjust famciclovir for immunocompromised patients and patients with renal impairment in a non-hospital setting.

· The benefit of oral treatment over topical therapy was not significant in the general population and there was merit in first treating herpes labialis topically and reserving oral treatment as a second line therapy.

· There was limited data on resistance to famciclovir in the community and down-scheduling did not reflect a good risk vs. benefit ratio. It was noted that virus resistance was normally tested in immunocompromised patients and may not have been specifically tested in the broader population. The Committee required additional information on the issues of a possible increase in resistance through wider community use and the implications of off-label use (e.g. for genital herpes).

November 2009 MCC consideration

The MCC concluded that famciclovir could be reclassified from prescription to restricted medicine when sold in packs of three tablets for the treatment of recurrent herpes labialis, provided Medsafe was satisfied that:

- the applicant had approached the Pharmaceutical Society requesting their input on the treatment algorithm and implemented any suggested changes; and
- a warning statement that treatment should not be repeated within seven days is included.

The MCC noted that the applicant also proposed the following:

Warning statements

- To be added to the pack: "Caution: If you have kidney disease check with your doctor or pharmacist before commencing treatment; and not recommended for patients under 18 years of age."

Three additional changes

- The name of the product to be marketed would help infer and reinforce the single dose concept;
- to supply every pharmacy with a training kit; and
- to develop patient education material aimed at making patients aware of the optimal time to treat cold sores and to speak to their pharmacist about all treatment options.

Treatment algorithm

- Designed to help pharmacists identify patients who might benefit from the appropriate cold sore therapy and to screen out patients who were unsuitable for OTC treatment, for example patients who may have impaired renal function or may be immunocompromised.
- The MCC noted that, while pharmacists may not always know if a person had renal impairment, if there was renal impairment present, accumulation would not occur from a single dose of famciclovir.
- The MCC also noted that some other medicines available without prescription used in multiple doses also have a caution for renal impairment.

February 2010 NDPSC meeting

Issue of resistance

- A Member asserted that as famciclovir is a prodrug of aciclovir (a Schedule 4 substance **except** in single preparations for the treatment of herpes labialis where the

risk of development of resistance is low) the propensity for resistance to famciclovir was unlikely.

- The NDPSC also noted the pre-meeting submission's claims that regular pharmacovigilance of resistance was being conducted. However, a Member asserted that pharmacovigilance would be unlikely to detect resistance and a lack of therapeutic effect could be associated with individual patient qualities rather than resistance.
- Another Member noted that the potential for resistance to famciclovir was previously assessed by TGA with favourable results.

Potential benefits of harmonising with the MCC

- A Member noted that, with access to GPs restricted in some communities, a Schedule 3 listing would assist in both facilitating immediate action to reduce infection and improving treatment compliance. Several Members further asserted that any reduction in infection also had a broader benefit in reducing subsequent infectivity in the general population.
- A Member also noted that Schedule 3 supply of famciclovir requires the involvement of a health professional which the Member asserted would be adequate to maintain the integrity of famciclovir use as a second line treatment.
- A Member additionally asserted that the risk vs. benefit profile of famciclovir was similar to that of aciclovir.
- Other Members contended that the benefit arguments were less convincing since it had not been established that the proposed famciclovir treatment had greater efficacy than existing treatments. Several Members disagreed with the argument in the pre-meeting submission that efficacy over existing treatments was not a requirement for down scheduling. While there seems to be a genuine need for some Schedule 3 systemic treatment, these Members asserted that demonstrated efficacy was a central pillar for any argument claiming improved benefit to public health.

The NDPSC also considered whether the concerns from the October 2009 consideration had been sufficiently addressed so as to support harmonisation with the MCC decision, as summarised below:

- Several Members asserted that a pre-meeting submission had provided further information appropriately addressing the concerns raised by the NDPSC during its October 2009 consideration. Other Members contended that, while expanding somewhat on the arguments considered at the October 2009 meeting, there was no substantially new robust information that would allay the concerns raised at that time.
- Members additionally noted that the MCC had not had the opportunity to consider the October 2009 NDPSC minutes prior to their decision on famciclovir.
- A Member also asserted that while harmonisation between NZ and Australia was a objective, it was not a requirement. Several Members also contended that the MCC's

decision to down schedule famciclovir was dependant on a number of NZ specific requirements (including development of an appropriate treatment algorithm), and argued that Australian jurisdictions may not be able to enforce these requirements to a similar degree.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that 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 (d) the dosage; formulation and presentation of a substance.

Members discussed the criteria for a Schedule 3 listing and agreed with the evaluator's recommendation to down schedule famciclovir single dose for the treatment of herpes labialis from Schedule 4 to Schedule 3. A summary of the discussion is provided below.

Members noted that in previous applications for down scheduling famciclovir single dose, the Committee's concerns were about the comparative efficacy between famciclovir oral vs. topical preparations, the potential for development of virus resistance caused by off label use of famciclovir for other forms of herpes, and the use by patients with renal failure.

Members also noted that the previous two evaluations supported a Schedule 3 entry for famciclovir for the treatment of herpes labialis, however, also asserted more data on the use by immunocompromised patients and the risk of virus resistance should be provided by the applicant. A Member noted that the mechanism of use (famciclovir as a pro-drug) mitigates this resistance concern, as famciclovir is not activated into penciclovir until taken into cells infected with the virus. The Committee generally agreed that the potential for development of resistance had now been sufficiently addressed and was no longer a significant concern.

Members generally agreed that in view of the data provided by the applicant and with resistance no longer being a major concern that a single dose preparation being a Schedule 3 medicine, was much more acceptable, noting the following:

- A Member stated that it would be attractive to have a medicine with systemic distribution available OTC for those who have frequent episodes of herpes labialis. Another Member asserted that a medicine with systemic effect was more effective than topical preparations in stopping the emergence of secondary lesions. The Member stated that data suggested that oral formulations would assist in limiting relapse of herpes labialis compared to dermal formulations.
- A Member also stated the importance of quick access to treatment during the prodromal phase of herpes labialis. A Member also asserted that having oral formulations available OTC would be beneficial where the use of topical formulation would not be appropriate i.e. lesions around the eyes.

- A Member noted a pre-meeting submission's comment that off label use of famciclovir was unlikely to be an issue, as it would be expensive for consumers to buy several packs for the treatment of other forms of herpes.

Members noted the evaluator's particular concern with chronic kidney disease (CKD) and discussed the following:

- A Member stated that the main risk of famciclovir use by renal impaired patients was systemic accumulation of the drug. Another Member contended that a single dose, did not seem to represent a significant risk to renal impaired patients, particularly in comparison to other medications currently available OTC, such as NSAIDs.
- A Member noted the risks of severe consequences of systemic drug accumulation related to aciclovir use by renal impaired patients for the treatment of viral encephalitis. Another Member, however, explained that the toxicity caused by aciclovir was due to individual drug sensitivities and such consequences were not likely for OTC famciclovir use.
- A Member asserted that in NZ the matter of renal impaired patients was carefully considered and there have been no issues in relation to renal impaired patients associated with OTC use of famciclovir single dose.

Members discussed the proposed pharmacist algorithm developed by the applicant. A Member stated that because famciclovir was off patent, there were generic products available in the market for which other sponsors may not provide a similar algorithm. The Member stated that too much emphasis should not be placed on the pharmacists' use of algorithm and, instead one should ensure that pharmacists should be able to provide correct advice and patient screening. A Member asserted that, as with other algorithms, the Pharmaceutical Society of Australia would produce a thorough protocol and training materials, using the substance name rather than a brand name, to assist pharmacists to identify and manage potential use in renal patients.

Members additionally noted the evaluator's points regarding use in immunocompromised patients, particular that such risks were largely mitigated by the single dose presentation and intervention by the pharmacist. A Member therefore stated, and the Committee agreed, that matters related to restricting the use of famciclovir to immunocompetent patients and certain age groups should be left to the regulator.

The Committee agreed to recommend a down scheduling of famciclovir to Schedule 3. Members also argued that, for clarity, the scheduling entry should include in brackets the word 'cold sores' after the term herpes labialis.

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) the purpose and extent of use; and (d) the dosage; formulation and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to reschedule famciclovir for oral use in divided preparations containing a total dose of 1500 mg or less of famciclovir for the treatment of herpes labialis (cold sores) from Schedule 4 to Schedule 3. The delegate decided that an implementation date of 1 May 2012 was appropriate (i.e. three months after the publication of the final decision).

Schedule 3 – New entry

FAMCICLOVIR for oral use, in divided preparations, containing a total dose of 1500 mg or less of famciclovir for the treatment of herpes labialis (cold sores).

Schedule 4 – Amendment

FAMCICLOVIR – Amend entry to read:

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

2.2.4 FOLLISTATIN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Follistatin – seeking advice on inclusion of follistatin in Schedule 4 or 8. Advice is also sought on the possible inclusion of a group entry for follistatin-related proteins in the same schedule.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended inclusion of follistatin in Schedule 4 and also recommended an entry in Appendix D, paragraph 5. The Committee recommended an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Follistatin is an autocrine glycoprotein occurring naturally in humans and animals. It is an activin-binding protein which may inhibit the anterior pituitary's secretion of follicle stimulating hormone (FSH). Specifically, follistatin is a natural antagonist of myostatin (a potent negative regulator of skeletal muscle mass). Follistatin has also been referred to as FSH-suppressing protein (FSP).

Follistatin was being investigated for its role in the regulation of muscle growth in mice, as an antagonist to myostatin, specifically in the treatment of spinal muscular atrophy (Rose *et al* 2009, available at www.ncbi.nlm.nih.gov/pmc/articles/PMC2649020/?tool=pmcentrez).

In July 2011, following reports of suspected abuse of follistatin, a delegate decided to initiate a consideration of the scheduling of follistatin. The delegate also decided that this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

SCHEDULING STATUS

Follistatin is not currently scheduled, nor does it appear to be captured by any group entry or as a derivative of a currently scheduled substance.

INITIAL SUBMISSIONS

The delegate sought advice on whether follistatin required scheduling (either inclusion in Schedule 4 or Schedule 8). In referring the matter to the ACMS the delegate noted that:

- Follistatin appeared to have abuse potential. There were reports noted by the TGA of misuse by body builders to increase muscle mass. The Secretariat also found a number of online references promoting the misuse of follistatin.
- There was limited information on the risks, benefits, potential therapeutic uses and extent of abuse of follistatin which would assist in determining the appropriate schedule into which follistatin could be listed. It was anticipated that public consultation and advice from ACMS could provide further information on these factors.
- There were a number of related online references to the misuse of "follistatin-related proteins".

There was no evidence of current legitimate therapeutic use for follistatin. However, there were online references to clinical trials starting from 2010 using follistatin in the treatment of spinal muscular atrophy.

October 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that 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 (e) the potential for abuse of a substance.

Schedule 4 vs Schedule 8

Members noted that follistatin was a member of the transforming growth factor beta superfamily, which included activin and myostatin. A Member queried the precedent for scheduling substances which occur naturally in the body and whether this could have an inadvertent regulatory impact. However, another Member noted that there were a number of substances which occur naturally in the body currently listed in Schedule 4 with no inadvertent negative regulatory effects.

Members noted that follistatin could potentially have a significant role in the treatment of disease conditions for which there have been limited advances. A Member queried whether scheduling would limit future research into therapeutic uses of follistatin. A Member asserted that substances used in clinical trials were normally treated as having at least Schedule 4-equivalent restrictions and scheduling was not expected to impact such research.

Members noted reports of misuse of follistatin and its abuse potential. A Member asserted that there was no evidence of dependency to warrant a Schedule 8 entry. The Member, however, noted concerns that follistatin was associated with significant biological changes in the body and was at risk of abuse by the bodybuilding community. Another Member also asserted that misuse of follistatin had the potential to extend outside of these subgroups to image conscious members of the public. Members also noted that there was limited experience with the use of follistatin in Australia and a lack of information on therapeutic and toxic dose. Members generally agreed that follistatin warranted a Schedule 4 entry.

Appendix D

Members then discussed the need for an Appendix D entry for follistatin. A Member noted similarities between follistatin and anabolic steroidal agents in their use patterns and potential for abuse and asserted that similar restrictions should apply. Members noted that anabolic stereoids were listed in Appendix D, paragraph 5 – poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription). The Member also asserted that an Appendix D entry would not affect clinical research as paragraph 5 allows for possession in such circumstances. Members agreed that follistatin should also be included in Appendix D, paragraph 5.

Additional group entry

Members also discussed the need for a group entry, noting online references to abuse of "follistatin-related proteins". A Member asserted that the term "follistatin-related proteins" was ambiguous and may inadvertently capture other proteins which were not of concern. Members noted that according to the SUSMP, listing a substance in a schedule also captures its analogues and derivatives, unless specified otherwise. A Member asserted that individually listing follistatin would be sufficient to ensure that appropriate controls were in place for follistatin-derivatives. Members agreed that a group entry was

not required, specifically noting that derivatives would be captured by the follistatin entry.

Implementation date

A Member noted that as there were no pre-meeting submissions for this matter it appeared that scheduling of follistatin would not have any inadvertent negative effects on existing unscheduled products. Members agreed that an early implementation date was appropriate (i.e. 1 May 2012).

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 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 (e) the potential for abuse of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include follistatin in Schedule 4. The delegate also decided to include follistatin in Appendix D, paragraph 5. The delegate additionally decided that an implementation date of 1 May 2012 was appropriate (i.e. three months following the delegate's final decision).

Schedule 4 – New entry

FOLLISTATIN.

Appendix D, paragraph 5 – New entry

FOLLISTATIN.

2.2.5 3, 4-METHYLENEDIOXYPYROVALERONE (MDPV)

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

3,4-Methylenedioxypyrovalerone (MDPV) – seeking advice on a proposal to include 3,4-methylenedioxypyrovalerone in Schedule 9 with a cross-reference from the common name MDPV to the 3,4-methylenedioxypyrovalerone entry.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 9 entry be created for

3,4-methylenedioxypyrovalerone. The Committee also recommended a cross-reference be included in the index of the SUSMP from the common name MDPV to the 3,4-methylenedioxypyrovalerone entry. The Committee agreed to an implementation period of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

3,4-Methylenedioxypyrovalerone (MDPV) is an alkaloid designer drug of the phenethylamine class that is structurally related to cathinone or N-ά-[methyl-3,4-methylenedioxy)phenethyl]hydroxylamine (MDMA) (Schedule 9). Cathinone is an active alkaloid found in the khat plant and is related to methamphetamine (Schedule 8). MDPV, MDMA, cathinone and methamphetamine act on dopamine release.

MDPV is also an analogue of pyrovalerone (Schedule 4), a psychoactive drug which is infrequently used due to problems with abuse and dependence. Pyrovalerone is a Schedule V controlled substance in the US and Class C category in the UK.

MDPV is a stimulant and was first seized in Germany in 2007. Recently (in March 2011) the US Drug Enforcement Authority noted that the abuse of MDPV was increasing, particularly in Europe and Australia.

XXXXX submitted an application regarding MDPV direct to the Scheduling Secretariat. A delegate agreed that this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

SCHEDULING STATUS

MDPV is not specifically scheduled. MDPV is an analogue of pyrovalerone and may be captured by the Schedule 4 entry. MDPV is also structurally related to cathinone, listed in Schedule 9. There is uncertainty as to which substance would capture MDPV as a derivative.

In NZ, MDPV is not specifically classified. Pyrovalerone and cathinone, however, are listed as Class B2 Controlled Drugs.

INITIAL SUBMISSIONS

Application

XXXXX requested that 3,4-methylenedioxpyrovalerone (MDPV) be included in Schedule 9 with a cross-reference in the SUSMP index from the common name MDPV to the schedule entry.

Members noted the following from the submission:

- There were no systematic trials of the effects of MDPV in humans. There were reports of misuse and abuse of MDPV. Anecdotal reports from the Internet and

published case reports indicate that MDPV may cause effects similar to methylphenidate (at lower doses) and amphetamine or cocaine (at higher doses).

- Access to MDPV has been controlled in the UK, some European countries and some states in the USA.
- There had been seizures of products containing MDPV in New South Wales, Western Australia and South Australia. There were reports of use of 'bath salts' in the UK, Europe and the USA.
- Commonly reported adverse effects include tachycardia, hypertension, restlessness and agitation. There had also been reports of paranoia and severe panic attacks associated with the use of MDPV. The psychoactive effects of MDPV desired by users include mental stimulation, increased concentration, sexual stimulation/aphrodisiac effects and mild empathogenic effects.
- The adverse effects of MDPV include hyperpyrexia, increased and/or irregular heart rate, headache, dyspnoea, bruxism, restlessness, anxiety, loss of appetite and gastrointestinal disturbances. Higher doses of MDPV had cause intense panic attacks in stimulant intolerant users. Users had reported psychosis induced by sleep deprivation and becoming addicted after using higher doses, or using at more frequent dosing intervals.

Applicant's specific arguments against Section 52E

a) Risks and benefits of the use of a substance

- Indicated that there did not appear to be any current legitimate therapeutic uses for MDPV. Reports from users warned about the ease of overdose (producing long lasting panic attacks), potency, and the dangers of regular and/or heavy use (with lasting consequences on cognitive function and affect).

b) The purpose and extent for which a substance is to be used

- Asserted that none of the cathinones had any recognised efficacy as a plant fertiliser, nor would they function as a bath salt.
- Noted that there had been seizures of MPDV in Australia (in New South Wales, South Australia and Western Australia). There was a recent seizure in South Australia of tablets containing MDPV which were thought likely to have been sold as a 'legal high' type product.
- Indicated that there had been an increase in the number of reports about use of 'bath salts' containing MDPV or 4-methylmethcathinone (mephedrone) to Poison Control Centres in the USA. There had been reports of abuse of new cathinone derivatives including MDPV in Sweden and Finland.
- Products marketed as 'bath salts', 'plant fertiliser', 'plant food' or 'research chemicals' which were sold via the Internet, at head shops and herb shops may contain various cathinones including MDPV and 4-methylmethcathinone

(mephedrone). [Members noted that a head shop was a retail outlet specializing in drug paraphernalia used for consumption of cannabis, other recreational drugs, legal highs, legal party powders and New Age herbs].

c) Toxicity of the substance

- Indicated that there was limited information available about the toxicological effects of MDPV. There were, however, anecdotal reports from the Internet and the few published case reports appear to be highly dose dependent.
- Noted that a report from Michigan in the US, provided details about 35 patients who had visited an Emergency Department (ED) in the period 13 November 2010 to 31 March 2011 after ingesting, inhaling or injecting recreational designer drugs sold as 'bath salts' and asserted that these products could contain stimulant compounds such as MDPV or 4-methylmethcathinone (mephedrone). Seventeen patients were hospitalised, of these nine were admitted to the Intensive Care Unit. One person was dead upon arrival at the ED. The toxicological report for the person who died revealed a high level of MDPV, along with cannabis and prescription drugs. Autopsy results revealed MDPV toxicity to be the primary factor contributing to death.
- Indicated that there had been reports in the US media about deaths in persons who had used 'bath salts'. A recent media report (9 April 2011) indicated that two men whose bodies were found in a forest in March 2011 had 'bath salts' in their system (the active substance in the 'bath salts' was not identified in the media report). The Coroner, however, declared that the deaths were due to hypothermia. Also noted that an article published on 12 May 2011 indicated that the death of a 42 year old woman who was an abuser of 'bath salts' prompted legislators in that state to move to prohibit MDPV and its derivatives.
- Also noted that the Finnish Poisons Information Centre reported 33 calls regarding exposures to MDPV during the period of January 2008 to October 2009. The substance was used intranasally, orally, rectally or intravenously. Doses used were 10 to 30 mg orally and 5 mg intravenously. Five of the patients required hospitalisation. All of them had tachycardia, agitation, dyspnoea and hypertension. Two of the patients had reduced level of consciousness, one of them had convulsions and required intubation.

d) The dosage formulation, labelling, packaging and presentation of substance

- Users of MDPV reported that 5 mg was an active dose and typical doses were in the range of 5-20 mg. The onset of effect was at 1 hour with a peak effect at 90 minutes (lasting 1 hour) and the come-down occured at 2.5 hours (lasting 1 hour). The effects and length of high vary with the dose and the individual (reportedly from 0 to 12 hours plus). Re-dosing in a single session was common. Methods of intake of MDPV include ingestion, insufflation, smoking, intravenous injection or rectal administration.

- Indicated that the 'bath salt' products suspected to contain MDPV, (e.g. Ivory Wave), were labelled as 'not for human consumption' and specifically warn against using the product as snuff. The ingredients listed on the packaging did not refer to MDPV. The instructions for use indicated that the product was concentrated, that for the first few hours the user should only use one application and there was no need for a second application for hours. The labelling strongly recommended that the bath salts were not mixed with other similar products and for health and safety reasons it was always best to stay away from alcohol and prescription medication, or be intoxicated when bathing using the product or any other bath salts sold on the website.
- Argued that the presentation of these products, labelled for use as 'bath salts', 'plant fertiliser', 'plant food' or 'research chemicals' potentially increased the risk of inappropriate use.

e) The potential for abuse of a substance

- There had been reports of intense cravings for MDPV by users not unlike those experienced by methamphetamine users, which resulted in larger doses being consumed, which could result in a difficult come-down.
- Indicated that there was reference to use and abuse of MDPV on various websites. Some users of MDPV reported developing cravings for MDPV. Noted that increases in tolerance with use were also reported.
- Asserted that there appeared to be a risk of abuse, including a risk that users would re-dose with the product resulting in excessive doses, with a difficult come down similar to that experienced with methamphetamine.

Other matters

- Noted that the UK, some European countries and several states in the US had prohibited or regulated the use of MDPV. The 31 March 2010 report of the UK Advisory Council on the Misuse of Drugs *Consideration of the cathinones* indicated that the harms associated with mephedrone and related cathinones were commensurate with the amphetamines and the substances in Class B. The Council recommended that the cathinones (including MDPV) be controlled as Class B substances under the *Misuse of Drugs Act 1971*.

[Members noted that the UK's *Misuse of Drugs Act 1971* determines three classes (A, B and C) of substances for misuse, based on the level of harm caused. For example Class A includes cocaine, methadone, morphine, MDMA, LSD, heroin; Class B includes codeine, some amphetamines; and Class C includes amphetamines, cannabis, benzodiazepines, buprenorphine].

- Indicated that following regulation of the cathinones in the UK, other substances such as naphthyl analogues of pyrovalerone had been marketed in the UK as 'legal highs'.

- Asserted that MDPV qualified for a Schedule 9 listing, as the structurally related substances cathinone and MDMA are listed in Schedule I to *the United Nations Convention on Psychotropic Substances 1971*, as well as in Schedule 9 of the SUSMP.

Members noted that strong opioid analgesics were listed as 'narcotics' under Schedule I of the *United Nations Convention on Psychotropic Substances 1971*, they were subject to a system of annual reporting on production, importation/exportation and inventory by the signatory countries. Inclusion in Schedule I is a Schedule 9 factor as set out in the Scheduling Policy Framework.

October 2011 Pre-meeting Submissions

A pre-meeting submission was received from the XXXXX The submission supported the inclusion of MDPV in Schedule 9. The submission also stated the harm associated with the use of this substance was documented in literature and it had no medicinal value.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (b) the purpose and extent of use; (c) toxicity; (d) dosage; formulation and presentation; and e) potential for abuse of a substance.

Members noted that there was no evidence of legitimate therapeutic use for MDPV. Members also noted the potency of the substance and the danger associated with heavy and repetitive use. A Member stated that MDPV had been a hot topic for discussions at recent conferences in toxicology. The Member advised the Committee that there were documented cases of psychosis and cerebral haemorrhage in MDPV users. A Member stated a recent letter to the New England Journal of Medicine about 'bath salts' intoxication noted that MDPV was the primary ingredient in these products. The letter warned clinicians to be aware that the severity and lethality from overdoses with these products often necessitated care and monitoring in an intensive care unit.. The Member also stated that there was also a concern about MDPV being marketed in a misleading way, e.g. 'bath salts'.

Members noted the international controls applied to MDPV, and agreed that MDPV should be listed in Schedule 9.

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 relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (b) the purpose and extent of use; (c) toxicity; (d) dosage; formulation and presentation; and e) potential for abuse of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to create a new Schedule 9 entry for 3,4-methylenedioxypyrovalerone. The delegate decided that an implementation date of 1 May 2012 was appropriate (i.e. three months after publication of the final decision). The delegate also decided to create a cross-reference in the index of the SUSMP from the common name MDPV to the 3,4- methylenedioxypyrovalerone entry.

Schedule 9 – New entry

3,4-METHYLENEDIOXYPYROVALERONE *(MDPV).

SUSMP Index – New cross-reference.

MDPV
See 3,4-METHYLENEDIOXYPYROVALERONE.

2.2.6 SYNTHETIC CANNABINOIDS

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Synthetic cannabinoids – the delegate is seeking advice on the appropriate scheduling of the following synthetic cannabinoids and classes of synthetic cannabinoids, in particular inclusion in Schedule 8 or 9 with the possibility of cut-offs to unscheduled for lower concentrations:

- Dibenzopyrans
- Cyclohexylphenols
- Naphthoylindoles
- Naphthylmethylindoles
- Naphthoylpyrroles
- Naphthylmethylindenes
- Phenylacetylindoles
- Benzoylindoles

The delegate sought advice on the potential unintended regulatory impact of this type of decision. The delegate also sought advice on alternate wording of the schedule entry to possibly refer to:'synthetic agonists of cannabinoid receptors or synthetic cannabinomimetics'; and/or

- 'substances intended to have a substantially similar pharmacological effect to tetrahydrocannabinols'.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the following groups of synthetic cannabinoids be included in Schedule 9 to capture any individual substances within that group which were not separately specifically scheduled:

- Benzoylindoles
- Cyclohexylphenols
- Dibenzopyrans
- Naphthoylindoles
- Naphthylmethylindoles
- Naphthoylpyrroles
- Naphthylmethylindenes
- Phenylacetylindoles

The Committee also recommended that a group entry for synthetic cannabinomimetics be included in Schedule 9 except where separately specifically scheduled. The Committee recommended that no cut-off to unscheduled be allowed for lower concentrations in any of the above entries.

The Committee recommended an implementation date of within six months of the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Synthetic cannabinoids (or synthetic cannabinomimetics) comprise a number of groups of chemically unrelated structures, all of which are functionally similar to the active principle in cannabis, delta-9-tetrahydrocannabinol (THC).

Effects of synthetic cannabinoids are due to their agonist activity at the cannabinoid receptors, CB1 and CB2. CB1 is the receptor thought responsible for the euphoric and psychoactive effects of cannabis. CB2 is mainly found in the immune system and may play a role in pain control as well as mood and behaviour regulation.

Many synthetic cannabinoids were synthetised with the aim of using them as a laboratory tool to identify marijuana receptors and to determine the mechanism of action of cannabis. Others have been developed as part of efforts to find new drugs for nausea, glaucoma and appetite suppression, but few appear to have moved past the preliminary testing stage. Synthetic cannabinoids may also be used in pharmacological studies involving structure-activity relationships, receptor binding studies and mechanisms of action studies.

Some synthetic cannabinoids have been used for medicinal purposes (e.g. nabilone – for the treatment of anorexia and to combat nausea in patients undergoing cancer treatments, and dronabinol – synthetically produced pure THC used in multiple sclerosis and pain patients).

Prior to July 2011, there were reports in Australia and overseas of a number of unscheduled synthetic cannabinoids being used recreationally as a 'legal' substitute for cannabis. These substances appeared to be added to (sprayed onto) mixtures of dried herbs which were then smoked in order to obtain an effect similar to cannabis. Use as a herbal tea was uncommon due to the lipophilic compounds' low solubility in water.

In May 2011, the WA State Drugs and Poisons Unit submitted a request for:

- A delegate-only final decision to include in Schedule 9 seven of the most commonly detected individual synthetic cannabinoids with demonstrated harmful effects or potential for significant harmful effects; and
- A referral to the ACMS for advice on the inclusion in Schedule 9 of broader synthetic cannabinoid groups.

In July 2011, the delegate decided to include eight synthetic cannabinoids in Schedule 9 (including all seven identified by the WA submission). The delegate also noted that the inclusion of these eight substances would capture other similar synthetic cannabinoids under the SUSMP's derivatives clause (see Part 1 – Interpretation, paragraph 1(2)).

The delegate also decided that a consideration of the scheduling of groups of synthetic cannabinoids would be referred to the October 2011 meeting of the ACMS for advice. Specifically, the delegate noted:

- the risk of users potentially moving onto substances within other synthetic cannabinoid classes not currently captured by these restrictions;
- that this could be addressed by listing the known classes of synthetic cannabinoids in Schedule 9 as group entries;
- that new classes of synthetic cannabinoids could be created for misuse purposes;
- certain jurisdictions had attempted to address this issue by inclusion of an outcome-based class entry either for "all synthetic agonists of cannabinoid receptors" or "substances intended to have a substantially similar pharmacological effect to cannabis"; and
- that advice from the public was required to identify any potential inadvertent impact of such group entry approaches.

SCHEDULING STATUS

There are several synthetic cannabinoids currently specifically listed in Schedule 4 (e.g. rimonabant), Schedule 8 (e.g. nabilone) and Schedule 9 (e.g JWH-018). These entries

also capture a number of other synthetic cannabinoids as derivatives in accordance with Part 1 (2) of the SUSMP.

A substance is not classed as a derivative on the basis of a single, prescriptive set of criteria. Classification of a substance as a derivative of a Scheduled poison relies on a balanced consideration of factors to decide if a substance has a similar nature (e.g. structurally, pharmacologically, toxicologically) to a Scheduled poison or is readily converted (either physically or chemically) to a Scheduled poison.

INITIAL SUBMISSIONS

May 2011 Western Australia Request

The original WA submission raised concerns that if only certain substances within each chemical group were scheduled, those manufacturing these products would move to a different compound that has similar pharmacological activity. There was evidence that this had occurred in other countries within weeks of the specific prohibition of certain individual synthetic cannabinoids.

The submission therefore requested that the following groups of synthetic cannabinoids be considered for inclusion in Schedule 9:

- Dibenzopyrans ('classical' cannabinoids) – e.g. HU-210 and HU-211, THC. (It was noted that due to their chemical structure, HU-210 and HU-211 could currently be captured through the derivatives clause by the Schedule 8 nabilone entry).
- Cyclohexylphenols ('non-classical' cannabinoids) – e.g. CP 47,497, Analog VII or cannabicyclohexanol.
- Naphthoylindoles – e.g. JWH-015, JWH-018, JWH-073, JWH-122, JWH-200, JWH-210, JWH-398 or WIN-55,212.
- Naphthylmethylindoles.
- Naphthoylpyrroles.
- Naphthylmethylindenes.
- Phenylacetylindoles – e.g. JWH-250 or JWH-251.

It was noted that although a similar group entry approach was used in the UK in December 2009 through their *Misuse of Drugs Act 1971*, other synthetic cannabinoids had since appeared in products within the UK which were not captured by these groups (see below for more information on UK controls).

Although there was a lack of evidence of industrial use for the compounds captured by the UK's broad scheduling approach, the submission noted that if the above group entries were included in Schedule 9, there may be potential for impact on future drug

development by pharmaceutical manufacturers. The request noted that referral of a proposal to schedule these group entries to the ACMS would be subject to public consultation which would help inform of any unintended consequences of the proposed scheduling.

The request also specifically addressed a number of matters under Section 52E of the *Therapeutic Goods Act 1989* (the Act), as summarised below:

(a) Risks and benefits (including toxicity)

- Some users of herbal smoking blends containing synthetic cannabinoids had reported similar effects to cannabis such as relaxation and sedation. Commonly reported effects included paranoia, anxiety, racing thoughts and irritability. Other effects included hallucinations, tremors, seizures, drowsiness, slurred speech, dilated pupils, elevated blood pressure, vomiting and chest pain. There were also reports of the use of synthetic cannabinoids precipitating the redevelopment of psychosis in patients with a history of mental illness (similar rates to those associated with cannabis use).
- The smoking of any substance is likely to have an adverse effect on health and, like the smoking of tobacco and cannabis, herbal smoking blends may put users at risk of developing pulmonary conditions such as chronic bronchitis and lung cancer. Another potential concern with these substances was the possibility of serotonin syndrome. The indole moiety in certain compounds in the JWH series results in a similar structure to serotonin and may increase serotonin receptor activation. (The delegate noted that the overall structure of the scheduled synthetic cannabinoids was sufficiently different so as not to inadvertently capture serotonin as a derivative).
- Claims had also been made in the media that herbal smoking mixtures allegedly containing synthetic cannabinoids were responsible for at least three deaths in the US. However, one of these deaths was subsequently shown to be the result of a 'mixed drug intoxication' and there was no coronial information available on the role of these products in the other two deaths.
- There was no scientific literature describing the long-term effects of either the synthetic cannabinoids themselves or the effects of smoking the herbal blends. The relatively short period of use within populations (probably since 2008) was insufficient to examine longer-term effects such as onset of mental illness and associations with cancer.
- There was a lack of peer reviewed literature of systematically conducted trials of either the toxicology or potential beneficial effects of these substances in man. There was limited animal toxicology data available for some synthetic cannabinoids. There was also little information about the potential health effects of the herbs used as carriers for the synthetic cannabinoids.
- Determining prevalence of use was hampered by difficulties in detecting both the parent compound and metabolites in urine samples and, prior to 2008, there was no mechanism for recording synthetic cannabinoid related admissions to health services.

In Australia, it was likely that hospital admissions would be recorded as relating to 'cannabis derivatives' and therefore it was not possible to ascertain the proportion of admissions due to these synthetic substances.

(b) Purpose and extent of use

- There was no evidence of legitimate human therapeutic use associated with the seven substances identified by WA. Although there were anecdotal claims of antidepressant, antinausea and pain relieving effects, the initial choice to use synthetic cannabinoids was almost always for the purpose of obtaining a psychoactive effect.
- It was suggested that use of these products was more popular in novice drug users hoping to get a 'high' while avoiding breaking the law. It could be suggested that this increases risk of use by younger persons.
- In WA, consumers indicated that they chose to use these types of preparations as an alternative to cannabis because the substances in these herbal smoking mixtures were not detected in drug screening tests used by their employers. Media reports from New Zealand (NZ) also indicated that employers were concerned about use of 'herbal highs' in high risk industries such as transport, civil engineering, aviation and mining.

(d) Dosage, formulation, labelling etc

- Herbal smoking products available at this time did not indicate which synthetic cannabinoids they contained or in what quantities. Packages generally contained 1 g or 3 g of crushed dried plant matter. Testing had shown that a product sold under the same brand at different times may contain different synthetic cannabinoids in varying quantities.

(e) Potential for abuse / misuse

- There were reports of patients meeting the standard criteria for both withdrawal and addiction in relation to use of certain synthetic cannabinoid herbal blends, with evidence of tolerance and withdrawal symptoms. Specific reports also suggested that JWH-018 was associated with drug tolerance, most likely due to receptor down-regulation. Receptor down-regulation combined with a drug's potential for psychoactive effects was believed to generally increase the likelihood of dependence on that drug.

United Nations Office on Drugs and Crime (UNODC) Report

The UNODC released a report on synthetic cannabinoids in herbal products focusing on the substances' pharmacological activity, potential toxicity and recommendations regarding their legal handling. The report made a number of points relevant to the consideration:

- Since 2004, herbal mixtures containing synthetic cannabinoids were available in several European countries. Initially, these products were not popular and were used by only a small group of experimental users. However, numerous reports on these

products surfaced in German newspapers and television in 2008 proclaiming their use as 'legal' cannabis substitutes, leading to dramatic increases in popularity.

- While these products were initially found to be popular among users of different ages and socioeconomic status, a recent survey suggested that the use of these products had dropped significantly. However, it was still increasingly popular among users who have to undergo regular urine drug screenings as current screening methods did not detect synthetic cannabinoids.
- In addition to the seven groups of synthetic cannabinoids requested by WA, the UNODC also provided details on the following synthetic cannabinoid groups:
  - Benzoylindoles (included in the delegate's referral for advice) – e.g. pravadoline, AM-694, RSC-4.
  - Eicosanoids (not included in the delegate's referral for advice) – endocannabinoids (substances produced from within the body that activate cannabinoid receptors) such as anandamide, and their synthetic analogues e.g. methanandamide.
  - Diarylpyrazoles (not included in the delegate's referral for advice) – selective CB1 antagonists e.g. rimonabant (listed in Schedule 4).
- Noted that synthetic cannabinoids commonly used in pharmacological studies included CP-55,940 (a cyclohexylphenol), WIN-55,212-2 (a naphthoylindole) and anandamide (an eicosanoid).
- Noted the adverse effects associated with use of synthetic cannabinoids, specifically the increasing numbers of hospitalisations with severe intoxications following use of products claimed to contain JWH-122.
- Stated that there was no valid data on the toxicity of these compounds so far, however it could be speculated that some of the metabolites, particularly those carrying a naphthyl moiety, may have carcinogenic potential.
- Stated that although cannabis had a comparatively low acute toxicity, at least some of the synthetic compounds recently considered could cause severe or life-threatening intoxications when overdosed, particularly those which act as full agonists at the CB1 receptor (HU-210, CP-55,940 or WIN-55,212-2).
- Noted evidence which suggested that a number of synthetic cannabinoids may have a higher addictive potential compared to cannabis due to quicker development of tolerance.
- Stated that the herbal blend phenomenon did not seem to disappear in countries which prohibited either single actives or groupings of synthetic cannabinoids, although the number of users may have been reduced due to lower availability and lesser media presence. Noted that there remained a variety of these products available on the Internet with new synthetic cannabinoids continuously appearing.

- Noted that the use of a generic definition for controlling synthetic cannabinoids would still bear the risk of not covering all possible derivatives and may possibly hamper synthetic cannabinoid research.

UK controls on synthetic cannabinoids

In 2009, the UK Advisory Council on the Misuse of Drugs (ACMD) released a report containing recommendations on major cannabinoid agonists (available at www.homeoffice.gov.uk/publications/alcohol-drugs/drugs/acmd1/acmd-report-agonists). The report concluded that the harms of synthetic cannabinoids were broadly commensurate with those of cannabis and that they should be classified accordingly.

The report also made the following points summarised below in relation to restrictions on groups of synthetic cannabinoids:

- Noted that specific control of substances offered the simplest approach, but not only would this require the listing of a large number of compounds by their systematic names, there was a risk that any such list would not be exhaustive. In other words, non-controlled (designer) analogues could rapidly appear on the illicit market.
- Stated that generic control would be appropriate for groups of substances where:
  - Relatively simple substitution patterns could occur in a structural nucleus.
  - A large number of examples were already known.
  - Synthesis of further analogues might be anticipated.
  - The target group could be encompassed with a simple definition.
- Suggested generic control for six of the seven major groups of synthetic cannabinoids also identified in WA's submission (cyclohexylphenols, naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes, phenylacetylindoles).
- Stated that although other miscellaneous synthetic cannabinoids were known, they were either weak agonists at the CB1 receptor or were receptor antagonists or mixed agonists/antagonists, hence would have little if any psychotropic actions and were not considered by the ACMD. A further complication with some cannabinoids was that they may show physiological effects unrelated to cannabinoid receptors.

In recent correspondence with the ACMD it was noted that the minor classes of synthetic cannabinoids (such as the benzoylindoles) were not included in their 2009 recommendations and a number of substances from these classes have since appeared in the UK. Members noted that the delegate's July 2011 decision to include AM-694 in Schedule 9 captured a number of benzoylindoles as derivatives.

Update on NZ restrictions

The NZ Parliament was considering an amendment to its Misuse of Drugs legislation to enable synthetic cannabinoids to be gazetted immediately upon identification, allowing removal from sale within seven days.

This change was an interim measure ahead of the proposed introduction of more extensive amendments, which would change the current onus of proof provisions in that legislation so that vendors of such products would be required to prove their products were safe for sale.

October 2011 Pre-meeting Submissions

Seven pre-meeting submissions were received from XXXXX

The submissions made the following points, as summarised below.

XXXXX

- Suggested that synthetic cannabinoids should be included in Schedule 8, not Schedule 9. Stated that there were no pharmacotherapies currently available for the management of cannabis withdrawal or dependence. Asserted that inclusion of synthetic cannabinoids in Schedule 8 would allow clinical trials for this indication. Noted that a clinical trial using nabiximols for management of cannabis withdrawal was currently being conducted.
- Stated that dibenzopyrans (under consideration), dronabinol and nabilone (both Schedule 8) had also shown promise for the management of cannabis dependence in addition to their use in the management of nausea and as an adjunct analgesic.
- Noted that synthetic cannabinoid receptor agonists were attractive to users of herbal cannabis who primarily seek the effects of THC. Also noted that synthetic cannabinoids also appeared to share similar harms compared to THC.
- Noted that there was limited evidence available on synthetic cannabinoids. Noted published case history reports on JWH-018's potential to precipitate psychosis in vulnerable individuals. Also noted a 2011 internet survey on use of herbal mixtures containing synthetic cannabinoids found that while most users did so out of curiosity and because they liked the effects, 40 per cent of the sample had negative or unwanted effects. Almost one third reported using synthetic cannabinoids to get intoxicated while avoiding detection in drug urinalysis testing in workplace or criminal justice settings.
- Stated that the current list of 8 classes of synthetic cannabinoids under consideration was comprehensive although not complete. Stated that the following synthetic cannabinoids were missing: JWH-171, JWH-176 and JWH-030. Members noted that JWH-030 would be captured by the proposed naphthoylpyrroles entry and JWH-176

would be captured by the proposed naphthoylindole entry. JWH-171 would only be captured by an outcome-based entry.

- Also recommended that both outcome-based entries should be adopted to reduce enforcement challenges, however noted that these may inadvertently capture other substances.
- Specifically noted that the term cannabinomimetic was also used to describe preparations of *Echinacea purpurea* and *Spilanthes acmella* that were said to have a high affinity for CBl and CB2 receptors and were reportedly used by body builders to stimulate appetite.
- Also stated that use of the wording "substances intended to have a substantially similar pharmacological effect to tetrahydrocannabinols" alone would be problematic. Stated that demonstration of the pharmacodynamics and pharmacokinetics of any product suspected of being a synthetic cannabinoid, would be challenging. Recommended that the onus of proof should be on the individual wishing to possess or sell the preparation that is suspected of being cannabis-like. Members noted that the legislation currently placed the onus of proof on the manufacturer/supplier of products.

XXXXX

- Supported inclusion of individual synthetic cannabinoids in Schedule 8 if appropriate therapeutic indications were identified during the consultation process. Otherwise supported inclusion of a group entry for synthetic cannabinoids in Schedule 9 with an exemption when separately specified in other Schedules.
- Raised concerns regarding the irresponsible use of synthetic cannabinoids obtained in the form of herbal smoking blends and stated that this abuse potential warranted inclusion of synthetic cannabinoids in either Schedule 8 or 9.
- Raised concerns regarding the marketing of synthetic cannabinoids as "safe and legal" alternatives to illicit drugs. Specifically raised concerns over the marketing of herbal smoking blends and its effect on smoking cessation outcomes at a time when there is a decline in people who are smoking.
- Questioned the need for an exemption from scheduling for lower concentrations. Raised concerns that such an approach may set a precedent for exempting other drugs from scheduling in lower concentrations. Stated that the abuse/misuse potential associated with cannabinoids did not warrant any scheduling exemption and if greater access was required for legitimate therapeutic purposes, consideration should be given to inclusion within Schedule 2, 3 or 4.

XXXXX

- Provided an update on WA state-based action on synthetic cannabinoids between June and August 2011. Noted that an interagency Government group, the WA Synthetic Substance Review Group was established to coordinate action and provide

advice to the WA Government about synthetic cannabinoids and other synthetic substances that may emerge.

- Noted that since the implementation of WA-based restrictions on synthetic cannabinoids there was a drop in the number of positive tests being detected from a range of employers across WA and across different industries, including mining, transport and various industry contractors. Specifically noted a decline in synthetic cannabinoid use from a peak of 16.3 per cent positive tests prior to 17 June 2011 (when the initial group of synthetic cannabinoids were prohibited in WA) to 2.1 per cent in the week following 5 August 2011 (when an additional 14 substances were prohibited in WA).
- Supported inclusion of the eight synthetic cannabinoid groups identified in the delegate's proposal in Schedule 9**.** Supported a precautionary approach towards new substances with the potential to cause harm. Stated that if there were any compounds with a legitimate therapeutic use that were inadvertently caught in this scheduling they could be dealt with on a case-by-case basis.
- Stated that synthetic cannabinoids did not appear to have any legitimate therapeutic use and the potential psychological and physiological harms of consuming these substances were unknown. Asserted that there were recorded and anecdotal examples received by the Synthetic Substance Review Group that supported users experiencing harms associated with the use of synthetic cannabinoid products.
- Stated that removing synthetic cannabinoids from legal sale and possession was expected to result in a significant decrease in consumption and the associated harm related to its use.
- Did not support use of the outcome-based entries listed in the delegate's proposal. Asserted that this approach would be unnecessarily burdensome to administer as it would be difficult to categorically designate compounds based on the receptor they act on, or that they had pharmacologically similar action to THC, particularly as they were essentially research chemicals that had not been comprehensively studied.
- Suggested that the delegate may wish to consider requiring manufacturers, distributors and retailers to prove that any new product containing a synthetic cannabinoid not captured in the eight classes of synthetic cannabinoids proposed for scheduling was safe for consumption and did not pose any reasonable risk of harm. Members noted that such regulator-type requirements were not currently addressed through scheduling.
- Stated that, from an operational perspective, it would simplify processes for Police if "synthetic cannabinoid" was a distinct drug category. Members noted that an entry for "synthetic agonists of cannabinoid receptors" would achieve the closest outcome to this suggestion, although this would not align with the above opposition to outcome-based entries.

XXXXX

- Did not support prohibition of synthetic cannabinoids. Suggested that synthetic cannabinoids should instead be regulated through licensing, age restrictions, labelling and restrictions over advertising to reduce risk to consumers.
- Noted reported cases of people suffering from symptoms such as heart palpitations, hallucinations and paranoia after consuming synthetic cannabinoids. Suggested that care needed to be taken in their use and that comprehensive research into the effects on short term and long term health was required. Stated that little was known about synthetic cannabinoids at this time, especially in relation to possible side effects, adverse reactions, potential for dependence, and other effects on humans.
- Noted that herbal smoking blend products sold provided little information on any of the ingredients and therefore users were unable to identify potential risks. Noted that products ranged in potency, substance's half life, their interaction with other substances, and variability in the product smoked with respect to the type of substance present and the concentration of the synthetic cannabinoid.
- Asserted that synthetic cannabinoids may be associated with an increase in comfort for patients with cancer or experiencing severe pain. Stated that research work was being undertaken to understand the potential benefits of synthetic cannabinoids and recommended that any scheduling of these substances should allow for their use in research.

XXXXX

- Did not support a broad scheduling approach to synthetic cannabinoids. Suggested that some synthetic cannabinoids should instead be regulated through licensing, age restrictions, labelling and restrictions over advertising to reduce risk to consumers. Recommended inclusion of most synthetic cannabinoids in Schedule 5 or 6. Recommended prohibition of pure powder forms of cannabinomimetic substances.
- Recommended that some compounds were of sufficiently low risk of harm or low concentration that no scheduling would be required. Stated that this would in general be restricted to CB2 selective compounds such as JWH-015 (a naphthoylindole) and JWH-133 (a dibenzopyran).
- Stated that some cannabinomimetic compounds that had become subject to human use were associated with a moderate risk of harm to an extent which would be difficult to minimise through the regulation suggested above. Recommended that the following substances remain or be placed in Schedule 9:
  - JWH-018 (currently listed in Schedule 9), due to issues with toxicity and abuse potential. Stated that this compound had proved unusually problematic and had a particular tendency to cause anxiety and serious adverse reactions, even when diluted in smoking blends.
  - HU-210 (currently captured by the Schedule 8 nabilone entry), due to its potency, severe side effects and a very long duration of action.

- AM-694 (currently listed in Schedule 9), due to toxicity concerns regarding its chemical structure.

· Asserted that synthetic cannabinoid products had been supplied to the public for a number of years without incident. Asserted that risks to public health of herbal smoking blends containing synthetic cannabinoids were generally low as the substances have been diluted with inert herbal material. Raised concerns regarding the public moving onto other "less safe" substances once synthetic cannabinoids are prohibited.

· Claimed that toxicological effects of the cannabinoids appeared to be minor, as few adverse health effects have been seen except in very heavy users. Asserted that anxiety and panic attacks were the only side effects commonly reported from diluted smoking blends, and usually occurred in inexperienced users who failed to follow dosage instructions or were not provided with information about usage.

· Claimed that synthetic cannabinoids had a very low potential to cause death in most cases. Stated that large overdoses of JWH-018 powder had produced effects such as panic attacks, vomiting, sudden loss of consciousness and even convulsions, which had not been seen with other related compounds. Asserted that to date were not aware of any deaths caused by these substances.

· Noted the lack of research available on these substances outside of anecdotal reports. Listed names of a number of studies investigating potential therapeutic uses of synthetic cannabinoids but did not provide copies of these studies in the submission.

· Noted that the majority of Australians who use these substances do so for recreational purposes. Asserted that recreational use was insufficient reason to schedule a substance. Asserted that allowing access through regulation would "not cause death or dependence and would be far safer than many legal products available over the counter now". The submission did not provide any examples of current over the counter products as comparisons.

· Stated that many substances which would be captured by the proposed group entries have no current use. Asserted that as the potency and toxicity of substances can vary within groups, scheduling of a group entry would result in harmless substances being incorrectly scheduled and impede research and development of therapeutic uses for these substances.

· Asserted that, broadly, the subjective effects of synthetic cannabinoids tend to correlate with their chemical structure, with compounds closer in structure to THC more accurately replicating the effects of cannabis. Stated that, for example, JWH-073 (the 1-butyl homologue of JWH-018) was 3-5x weaker by weight and had a substantially lower "ceiling" on maximal effects, despite differing by only a single CH_2 repeating unit in the length of the indole 1-alkyl side chain, while JWH-019 (the 1-hexyl homologue) had around 75 per cent the potency of JWH-018 but with similarly weaker subjective effects.

- Stated that some weaker compounds such as WIN 55,212-2 appeared to have substantially lower efficacy as partial agonists than THC, and produced only weak cannabinomimetic effects with a low ceiling on maximum activity and no further increase in effects once this was reached, no matter how large a dose was taken. Asserted that these were not considered useful for smoking blends, but may have other potential applications and were considered to be of 'low risk of harm'.
- Asserted that synthetic cannabinoids were in most cases unable to induce physical or psychological dependence comparable to that of cannabis, aside from some specified compounds such as JWH-018, (C8)-CP 47,497 and HU-210 which may produce physical or psychological dependence similar to or greater than that of cannabis following prolonged heavy undiluted use.
- Provided suggestions on limiting access to synthetic cannabinoid products through restrictions on advertising, types and locations of supply venues, age of consumers, labelling and dosage and monitored similar to TGA monitoring of "herbal" aphrodisiac products. Provided a number of examples of maximum dosage concentrations per gram of smoking blend:
  - (C8)-CP 47,497 at 50 mg/g.
  - JWH-073, JWH-019 or JWH-081 at 100 mg/g.
  - JWH-250 or 1-pentyl-3-(4-methoxynaphthoyl) at 150 mg/g.
- Claimed that although reports of abusive use and adverse reactions had been publicised, these were rare in the context of the overall number of users. Stated that these reports tended to be restricted to use of either pure powder forms of the drugs, or smoking blends containing high concentrations of the strongest synthetic cannabinoids (e.g. JWH-018). Asserted that no peer-reviewed research had been conducted on abuse potential of synthetic cannabinoids.
- Made additional non-scheduling recommendations regarding the importation of synthetic cannabinoids and manufacturing locations.

XXXXX

Members noted that many of the comments in this pre-meeting submission referred to the use of the cannabis plant, not just synthetic cannabinoids.

- Objected to inclusion of synthetic cannabinoids in Schedules 8 or 9. Claimed that such a decision would remove these substances from research due to bureaucratic requirements on laboratories. Recommended removal of previously listed cannabinoids, including cannabis, from Schedule 9 and instead apply regulation through licensed premises.
- Queried regarding the risk of harm associated with cannabinoids compared to other substances and products currently accessible to consumers (e.g. alcohol, tobacco, coffee).

- Commented on the rates of use of cannabis and synthetic cannabinoids in WA and cannabis smoking methods. Asserted the benefits of use of cannabis and cannabinoids in palliative care and antineoplastic research.
- Asserted that use of the term "'substances intended to have a substantially similar pharmacological effect to tetrahydrocannabinols" was too broad. Raised concerns regarding the ambiguous nature of such an entry and the level of public awareness of what was being prohibited. Asserted that implementation of such legislation relied on the enforcers' interpretation of "effect" and "similar to" which may be confused with effects of other substances such as tobacco or alcohol.
- Raised concerns that arrests based on observation of effect could be subject to abuse. Raised concerns regarding use of this approach for effects from other substances (e.g. nutmeg nuts which have been grated and smoked, "lions' tail" and some culinary plants).

XXXXX

- Objected to inclusion of synthetic cannabinoids in Schedules 8 or 9. Suggested creation of a new Schedule for "low-risk inebriants" – substances with no therapeutic value. Recommended that supply be restricted to over-18s and vendors be subject to licence and training requirements. Recommended adoption of the NZ "Schedule D" as a model approach. Members noted, as outlined in sections above, NZ was considering an amendment to its Misuse of Drugs legislation to remove such an option.
- Noted the lack of knowledge regarding the safety of synthetic cannabinoids and recommended further research. Asserted that existing anecdotal and internet information gave a good indication of the substances' safety. Asserted that a "dangerous until proven otherwise" approach was not appropriate for the scheduling of new substances.
- Noted that in high doses these substances appeared to have similar psychological effects to cannabis (paranoia, anxiety, emotional disturbance). Asserted that the potential for unpleasant side effects in excessive doses should not form the basis for prohibition of a substance.
- Stated that synthetic cannabinoids were not genotoxic nor cytotoxic. Stated that no organ toxicity was detected at doses of 10 mg/kg/bw in rats.
- Asserted that there had been no fatalities associated with the use of synthetic cannabinoids. Claimed that the recently reported death of a man following consumption of a product containing synthetic cannabinoids was due to unrelated causes.
- Asserted that synthetic cannabinoids could potentially be beneficial in the treatment of cannabis addiction and chronic pain and recommended further study.
- Asserted that it appeared that synthetic cannabinoids were non-addictive. Asserted that while repeated and consistent use of JWH-018 did lower sensitivity, no addiction

had been reported according to a published study. Stated that no build-up of the substance had been shown to occur in the body and its metabolism and excretion "occurs normally".

- Asserted that the proposed scheduling would be counter-productive, would not reduce risks to public health, but instead encourage misuse of synthetic cannabinoids. Raised concerns regarding new substances being created with greater negative side-effects.

Other matters

Queries on synthetic cannabinoids

Following the July 2011 decision, the Secretariat received numerous queries on the scheduling of other synthetic cannabinoids which were not specifically listed.

In most cases the relevant synthetic cannabinoid was sufficiently similar in structure to a scheduled substance to be considered a straightforward derivative. There was a limited number of queries where there was any ambiguity regarding whether the synthetic cannabinoid would be captured in Schedule 9 as a derivative (the only substance where ambiguity was identified was pravadoline [a benzoylindole], which is structurally related to AM-694).

The Secretariat did not receive any queries on synthetic cannabinoids which would not be captured by one of the eight substance group entries included in the delegate's proposal.

Possible cut-off to unscheduled

According to the SUSMP, an exemption to unscheduled exists for substances listed in Schedules 2 to 6 at concentrations below 10 mg/kg (0.001 per cent). This automatic exemption does not extend to substances listed in Schedule 9, where even small traces of the substance would be captured by the schedule's associated restrictions.

In referring this matter to the ACMS, the delegate noted that the current tetrahydrocannabinols Schedule 9 entry includes a cut-off to unscheduled for 50 mg/kg or less of tetrahydrocannabinols when not for internal human use. The delegate's proposal also sought advice on whether a similar exemption for the eight groups of synthetic cannabinoids would be appropriate.

The record of the May 1998 NDPSC meeting where the THC exemption was agreed indicated that it was to allow hemp seed oil and products containing hemp seed oil (which would contain trace amounts of THC) to be marketed.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that 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 (e) the potential for abuse of a substance.

Chemical group entries

Members noted reports of adverse reactions for synthetic cannabinoids, including the common symptoms of anxiety and increased heart rate. A Member noted that these substances were also associated with reports of psychosis in previously stable mental health patients. A Member asserted that these reports contradicted the unsubstantiated safety statements provided in some pre-meeting submissions received for this meeting. The Member noted that although a link between these substances and death had not yet been proven, there were currently no studies available on the long-term effects of synthetic cannabinoids.

A Member noted that when these substances were first synthesised, they were never intended for human use. Members also noted that apart from a number of specifically scheduled cannabinoids, there were no current legitimate therapeutic uses for any of the groups of synthetic cannabinoids included in the delegate's referral. A Member asserted that if a legitimate therapeutic use was later discovered, the specific substance could then be downscheduled. Members agreed that the eight chemical groups in the delegate's referral should be scheduled.

Members then discussed which schedule would be appropriate for these eight chemical groups. A Member asserted that enforcement of restrictions on these substances would be similar regardless of whether they are included in Schedule 8 or 9. The Member asserted that the main difference between Schedule 8 and 9 was the message regarding whether a current therapeutic use had been established. Members also noted that a Schedule 9 entry would still allow access to the substance for medical or scientific research as well as for analytical, teaching or training purposes with the approval of Commonwealth and/or State or Territory Health Authorities. Members generally agreed that Schedule 9 was appropriate for the synthetic cannabinoid group entries.

Potential cut-off to unscheduled

Members noted that there appeared to be wide variability in the potency of different synthetic cannabinoids (both within and across the different groups) and there was limited information which could inform an appropriate cut-off. A Member also asserted that minute quantities of these substances were still associated with a psychoactive effect. Another Member noted that a cut-off would be difficult to enforce as police would be required to undertake complex quantitative analysis to ascertain the legal status of a product. Members generally agreed that a cut-off for synthetic cannabinoid groups was not appropriate.

Outcome-based entries

Members discussed the benefits and difficulties surrounding implementation of outcome-based entries such as "synthetic agonists of cannabinoid receptors or synthetic cannabinomimetics". A Member noted that an outcome-based entry could be ambiguous and burdensome for law enforcers to administer. However, another Member asserted that inclusion of an outcome-based entry (such as one based on the mechanism of action of synthetic cannabinoids) would be of some benefit as it would send an appropriate message regarding these substances. The Member stated that it would also serve to further strengthen the enforcement basis for each of the individual group entries. A Member noted that internationally, several countries employed outcome-based entries to restrict specific substances. Members generally agreed that an outcome-based entry should be included in Schedule 9.

Members discussed the specific wording of the outcome-based entry. A Member noted that an entry for "substances intended to have a substantially similar pharmacological effect to tetrahydrocannabinols" would not be very helpful as pharmacological similarities to scheduled substances were already captured under the SUSMP's derivatives clause and this could also potentially capture non-synthetic substances that were beyond the scope of the current consideration. A Member asserted and others agreed that a Schedule 9 entry for "synthetic cannabinomimetics" would most accurately capture the intent of the decision with minimal risk of inadvertent regulatory impact.

Members also agreed that such an entry would make it explicitly clear that all synthetic cannabinoids (except where specifically scheduled) were to be considered Schedule 9 substances. This would limit the promotion of "new legal mixes" containing synthetic cannabinoids which may not fall into the above eight chemical group entries. Members agreed that communicating this position would act as a safety net allowing time for consideration of new synthetic cannabinoid chemical entries without the need for ongoing urgent scheduling action.

Implementation date

According to the timetable of delegate's decisions for matters referred to an advisory committee, an interim decision on this matter was expected to be published on the TGA website on 21 December 2011 with a final decision published on 1 February 2012.

Members agreed on an early implementation date of within 6 months of the publication of the delegate's final decision. Members noted that according to the timetable the earliest SUSMP Amendment implementation date following the publication of a final decision would be 1 May 2012 and agreed to recommend that this date would be appropriate for the delegate's decisions on synthetic cannabinoids.

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) the purpose and extent of use; and (e) the potential for abuse of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to create a group entry for all synthetic cannabinomimetics except when separately specified. The delegate also decided that the following groups of synthetic cannabinoids be specifically included in Schedule 9 and capture any individual substances within that group which are not separately specifically scheduled. The delegate decided that an implementation date of 1 May 2012 was appropriate (i.e. three months after publication of the final decision).

Schedule 9 – New entries

BENZOYLINDOLES **except** when separately specified in these Schedules.

CYCLOHEXYLPHENOLS **except** when separately specified in these Schedules.

DIBENZOPYRANS **except** when separately specified in these Schedules.

NAPHTHOYLINDOLES **except** when separately specified in these Schedules.

NAPHTHYLMETHYLINDOLES **except** when separately specified in these Schedules.

NAPHTHOYLPYRROLES **except** when separately specified in these Schedules.

NAPHTHYLMETHYLINDENES **except** when separately specified in these Schedules.

PHENYLACETYLINDOLES **except** when separately specified in these Schedules.

SYNTHETIC CANNABINOMIMETICS **except** when separately specified in these Schedules.

2.2.7 PIPER METHYSTICUM (KAVA)

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Piper methysticum (kava) – seeking advice on a proposal to allow access when used in accordance with the traditional use patterns of the Pacific Island region. Consideration may include exempting *Piper methysticum* from scheduling controls when in aqueous preparations for human non-therapeutic use (i.e. for recreational use).

The delegate is particularly seeking jurisdictional views in this matter and advice on alternate jurisdictional controls separate from scheduling which could be applied to appropriately control access and use of these kava preparations.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the scheduling of *Piper methysticum* (kava) remain unchanged and that kava in aqueous preparations for human non-therapeutic use remain as Schedule 4.

BACKGROUND BACKGROUND

Kava (*Piper methysticum*) is a plant native to the Pacific Islands that has been used as a ceremonial and relaxing drink by people of this region. The traditional kava drink is prepared from water extracts of the raw kava root or rhizome.

The active components in the kava root (kavalactones) have sedative, anxiolytic and central nervous system relaxant properties. Because of these pharmacological actions, kava products have been developed by pharmaceutical and complementary product companies for use as herbal anxiolytic agents. These usually contain ethanolic or acetonic extracts of kava in tablet or capsule form.

In October 2003, the National Drugs and Poisons Schedule Committee (NDPSC) decided that there was a need to restrict the use of alcohol/acetone extracts of kava, including those for bulk supply to health care practitioners, due to the potential risk of liver toxicities.

In June 2004, the NDPSC agreed to include kava in Schedule 4 with specific exemptions. The decision made all kava Schedule 4 except dried whole or peeled rhizome, its aqueous dispersions or extracts, tablets of 125 mg or less of kavalactones per tablet, teabags of up to 3 g kava, and not more than 25 mg of kavalactones per dose.

The June 2004 NDPSC record also noted that Standard 2.6.3 of the Food Standards Australia New Zealand's (FSANZ) Food Product Standards was to be retained to operate in conjunction with the National Code of Kava Management, including its prohibition in relation to mixing of kava with other foods (other than in those foods regulated under the New Zealand Dietary Supplement Regulations 1985). It was also noted that Standard 2.6.3 was amended to allow kava for use as a traditional beverage but the use in food of extracts prepared by organic solvent extraction would be prohibited and that labelling requirements would ensure the safe use of kava by consumers. FSANZ also advised that the foreshadowed decision to include non-aqueous extracts of kava in Schedule 4 of the then SUSDP (now SUSMP) was consistent with the amendments made to Standard 2.6.3, and was not expected to have any impact on the sale or supply of kava as a food. Details of current FSANZ regulations on kava are provided under the "FSANZ Regulation" heading below.

In October 2007, the NDPSC reconsidered the restrictions for kava and concluded in February 2008 that due to the potential for abuse and the hazard to public health of the whole or peeled rhizome, this form of kava should no longer be exempt from scheduling. The NDPSC specifically noted reports of significant overuse/abuse of kava, particularly in some NT communities. The NDPSC therefore amended the Schedule 4 entry so that only some products on the ARTG were exempt from scheduling.

In June 2009, the NDPSC considered a submission requesting kava be again exempt from scheduling when prepared as a traditional Pacific Islands drink and as dried fresh or frozen rootstock. The NDPSC again noted the significant reports of abuse and agreed that the submission had not established a case for overturning the previous decision to restrict access to kava products.

ACT Health submitted a request to reconsider the scheduling of kava aqueous preparations. A delegate agreed that this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

SCHEDULING STATUS

Kava in preparations for human use is listed in Schedule 4 with exemptions for select preparations included on the Australian Register of Therapeutic Goods (ARTG).

INITIAL SUBMISSIONS

Request

ACT Health requested an exemption from scheduling for aqueous extracts of the kava root or rhizome for human use, when prepared and used in accordance with the traditional customs of the Pacific Island region. The following SUSMP wording was suggested:

- "Aqueous extracts of the kava root or rhizome, when prepared and used in accordance with the traditional customs of the Pacific Island region."

or with reference to the Customs (Prohibited Imports) Regulations 1956:

- "When used in accordance with the importation of a quantity not exceeding 2 kg kava per person in the accompanied baggage of an incoming passenger (aged 18 years of over) to Australia."

The request also noted various points as summarised below:

- Kava had been subject to increased regulatory controls over the past decade, both within Australia and internationally due to reports of liver toxicity associated with kava products. Many European countries banned medicinal kava preparations from 2002. The *Northern Territory Kava Management Act* was passed to control local supply to mitigate reports of abuse of kava.

- Asserted that disparity existed between the schedule entry and Australian customs law. Specifically that, although it is possible to import up to 2 kg of the root per person, possession or use of that root was subject to penalties under State and Territory medicines laws. Raised concerns that this issue may not have been addressed by the NDPSC in delivering their 2008 decision.
- Concerns were raised amongst Australians of Pacific Island origin in the ACT that the current scheduling restrictions for kava deny them of their cultural practices. Strong concerns were directed to the ACT Minister for Health following advice that supply of kava at the 2011 National Multicultural Festival (NMF) was not permitted.
- Stated that the current scheduling for kava placed an unreasonable restriction on the traditional practices of the Australian Pacific Island community and that the application of national scheduling laws was too broad a tool to regulate against a localised problem in NT communities.
- Suggested that it would be more appropriate to apply State and Territory restrictions to address local concerns of abuse and misuse.

(a) Risks and benefits

- Stated that in considering the risks associated with kava use, it was important to distinguish between the hazards of hepatotoxicity at standard doses and the overall public health and social consequences of excessive use.
- Noted that the absolute risk of kava-induced hepatotoxicity was as yet unknown. Further points regarding liver toxicity are provided in the Toxicity section below.
- Also noted the overall health effects associated with heavy kava use (aqueous extracts) as seen in NT communities include a scaly, dry, flaking rash 'kava dermatitis', weight loss, raised gamma-glutamyl transferase (GGT – liver enzyme) levels, nausea, loss of appetite, conjunctivitis, impotence, general poor health, raised cholesterol, loss of time and money and decreased motivation. Asserted that these effects were reversible.

(b) Purpose and extent of use

- Noted that kava has been used as a relaxing and ceremonial drink to mark special occasions by a number of Pacific Island cultures. Also noted that in the past, it had also been served to the public at the NMF in the ACT.

(c) Toxicity

- Stated that according to the 2007 World Health Organisation (WHO) report on kava use, the risk of kava induced hepatotoxicity was higher with ethanolic and acetonic extracts. However, noted that some isolated case reports also linked the use of traditional kava extracts with liver damage.

- Stated that several risk factors for kava-induced liver toxicity had been postulated; including pre-existing liver disease, ethnic origin, combination with alcohol, co-medication, quality of the kava root, daily overdose or prolonged use.
- Noted that several reviews of the literature had emerged following the 2007 WHO report and the 2008 scheduling decision. Specifically noted that a 2010 review concluded that hepatotoxicity occurred independent to kava extraction method and may be primarily attributed to daily overdose or prolonged treatment, poor quality of the kava root and co-medication.
- Also noted a 2011 review which stated that the health effects of kava relating specifically to aqueous extracts, where the authors cite a moderate body of evidence associating kava use with raised GGT levels and conclude that the effect was dose related and reversible. Noted, however, that the review found no evidence of association between aqueous kava consumption and liver toxicity or permanent liver damage, even though this was widely described for ethanolic extracts.
- Asserted that according to a 2004 Fiji pilot study, even high doses of aqueous kava extracts did not reveal a trend towards liver toxicity. Noted that the study reported that the average number of kava bowls consumed in a lifetime by participants was 100,000 with no association with liver disease.
- Stated that even when taking into account isolated case reports of toxicity seen with traditional kava extracts there remained a lack of strong evidence that use of traditional kava extracts is associated with long term toxicity. Asserted that it may therefore be reasonable to conclude that traditionally prepared aqueous extracts did not present a risk of serious liver damage.

(d) Dosage, formulation, labelling, packaging and presentation of a substance

- Noted that the traditional kava drink is prepared by extracting the ground kava root or rhizome into water, which is then consumed in approximately 100 mL measures. Noted that kava root powder may also be used, where it was estimated that 100 g of dried powder was equivalent to 500 g of fresh root.
- Noted that it was difficult to estimate the total amount of kavalactones that would be present in a standard kava bowl due to the nature of its preparation. The concentration of kavalactones was likely to depend on many variables including the quality and age of the kava root, plant cultivar and whether the root is peeled, dried or whole during extraction. One study supported the use of particular plant cultivars and extraction methods that were less likely to cause hepatotoxic reactions.
- Stated that an estimated 500 g of the fresh root commonly drunk in Vanuatu would contain between 10-l5 g of kavalactone resin. Others estimate that approximately l kg of fresh root would be used to make 6-10 serves of kava in Vanuatu kava-bars.

(e) Potential for misuse/abuse

- Stated that there was good evidence for the adverse public health and social effects of excessive kava use, particularly in the Australian Aboriginal context, most notably in the NT. Asserted that the severe health and social problems experienced in the NT were well recognised and were not under review for the purpose of this submission.
- Stated that Pacific Island cultures were also not immune to problems associated with abuse or misuse. Noted that concerns were raised regarding kava use in these nations following modern Western influence and the commercialisation of kava use. Specifically noted that commercial 'kava-bars' were a common feature in places such as Fiji or Vanuatu and were associated with heavy use of kava in these countries.
- Noted that a cultural shift from the primarily ceremonial use of kava towards it being consumed as a social beverage much like alcohol in Western countries had also been observed.
- Stated that, however, concerns of abuse or misuse of kava amongst traditional users in Australia had not been reported.

(f) Other matters

- Asserted that compliance with the Schedule 4 requirements for kava extracts was unachievable, as it would not be reasonable for a doctor to issue a prescription for a non-standardised, nonmedicinal herbal drink, nor could it be argued that it is within their scope of practice. Noted that the Schedule 4 listing therefore effectively prohibited the use of traditional kava extracts in Australia.

FSANZ Regulation

The current FSANZ Foods Standard 2.6.3 for kava states:

> **2 Prohibition**
>
> (1) *Piper methysticum* (kava) or any derived substance must not be sold unless it is –
>
> (a) a beverage obtained by cold water extraction; or
>
> (b) the dried or raw form
>
> of the peeled root or peeled rootstock of plants of the species *Piper methysticum*.
>
> (2) Kava must not be used as an ingredient in foods.
>
> …

The Standard specifically notes that it should be considered in conjunction with State and Territory restrictions on the supply of kava; where kava is permitted for supply, the

requirements in the Standard complement those restrictions. Members noted that currently Australian jurisdictions did not allow the supply of kava as a food. Members discussion of whether kava could be considered a food is provided under the Expert Advisory Committee Discussion section below.

October 2011 Pre-meeting Submissions

Two pre-meeting submissions were received from XXXXX (a Clinical Research Fellow at XXXXX and XXXXX Both submissions supported the proposed exemption.

XXXXX

This pre-meeting submission made a number of points, as summarised below:

- Stated that XXXXX has researched, published and presented on kava. Noted that kava use was divided into:
  - medicinal use – i.e. tablets for anxiety (asserted that the current law for this use was adequate and well-balanced);
  - cultural use – i.e. traditional use by Pacific Island communities (asserted that the lack of a current law to protect this cultural use needed to be addressed); and
  - recreational use – i.e. use by people for enjoyment and sometimes abused by some communities (asserted that the current law for this use was unbalanced where its prohibition by certain states penalised those who use kava occasionally as a substitute for alcohol).
- Asserted that the current laws appeared to not be entirely working as there were some reports of kava abuse combined with alcohol by some Aboriginal communities. Stated that this remained a public health issue, noting the high black market cost of kava.
- Proposed that the 2 kg personal importation limit be replaced with a 5 kg allowance. Also suggested that Island Kava clubs or licensees should be allowed to import dry raw kava into Australia.
- Supported an opening up of kava sales to WA and to the ACT. Stated, however, that in the NT an alteration of the kava law should be met with greater vigilance in its prohibited use in "dry communities" with harsher penalties for black market sale.
- Also suggested education campaigns and the potential inclusion of a law to restrict kava drink driving. Suggested an estimated limit of less than 5 bowls or 500 mg of kavalactones for any such law, noting that greater kava use may inhibit motor skills.

The submission also provided a copy of the following publications:

- An article supporting the use of particular plant cultivars and extraction methods which may be less likely to cause hepatotoxic reactions. This article was also referred to by the ACT submission.

(Teschke, R., Sarris, J. &lebot, V. 2011, 'Kava hepatotoxicity solution: A six-point plan for new kava standardization', *Phytomedicine*, 18, 96-103.)

- A review of the efficacy safety and psychopharmacology of kava in relation to its use in psychiatry to treat Generalised Anxiety Disorder (GAD). The review made suggestions to limit the safety issues associated with use of aqueous kava by avoidance of use with alcohol, avoidance of high doses if driving or operating heavy machinery and recommending routine liver function tests for regular users.
  (Sarris, J., LaPorte, E. & Schweitzer, I. 2011, 'Kava: A comprehensive review of efficacy, safety and psychopharmacology', *Australian and New Zealand Journal of Psychiatry*, 45, 27-35.)
- A report on the Kava Anxiety-Lowering Medication (KALM) project which used an aqueous rhizome kava extract in GAD patients. The report focuses on the medicinal use of kava only.
  (Sarris, J., Teschke, R., Stough, C., Scholey, A. & Schweitzer, I. 2011, ' Re-introduction of Kava (*Piper methysticum*) to the EU: Is There a Way Forward?', *Planta Medica*, 77, 107-110.)

XXXXX

The pre-meeting submission consisted of a Kava Proposal document also submitted to the ACT Government and a document titled "*Guidelines for an Educational-Cultural Program on Kava*". The Kava Proposal document made a number of points, as summarised below:

- Asserted that kava use among Moanan/Pacific Island migrants in Australia was associated with a number of social and cultural benefits and positive behaviour patterns. Asserted that there were financial benefits to communities in allowing access to kava preparations.
- Claimed that the controversy surrounding cultural use of kava was a consequence of use of therapeutic kava tablets. Asserted that these two issues should be separately addressed.
- Stated that kavalactones extracted using some substances (e.g. acetone and ethanol) could cause health problems and/or death. Claimed that kavalactones mixed with other substances could react in the bodies of non-Moanan people causing health problems/death due to genetic reasons.
- Asserted that traditional Moanan methods of mixing kava with water were not associated with these risks. Stated that kava prepared by traditional Moanan methods could cause health and social problems if misused, similar to other substances (e.g. coffee, butter).
- Made comparisons between the health risks and uses of kava and other substances (alcohol, tobacco).

- Asserted that kava tablets could assist relaxation and cure depression and anxiety if used in wise and moderate manners and in accordance to correct health instruction and traditional Moanan knowledge and wisdom. Stated that these tablets could otherwise cause health problems and/or death. Claimed that the current kava restrictions dealt largely with control of marketing of kava tablets but not with kava in traditional use.
- Asserted that prior to allegations of its misuse by Aboriginal people in NT, traditional kava consumption was never associated with abuse.
- Asserted that the importance of kava in traditional Moanan culture was not considered when kava restrictions were decided.
- Stated that kava could be mixed with water in different degrees of dilution in accordance to the nature of the ceremony. Stated that according to Moanan traditions, there were approximately 40 different kinds of kava ceremonies. Stated that certain kava preparations were also used therapeutically in accordance with Moanan tradition.
- Stated that there was insufficient research regarding the "social, political, economic, moral, religious, medicinal, therapeutic and cultural significance" of kava ceremonies among Moanan migrants in Western societies. Stated that since the 2009 commercial ban there was a shortage of kava supply for Moanan people in Australia.
- Claimed that the ban of kava was a violation of human rights, cultural rights and "the UN Charters of Human Rights, Global Democracy and Indigenous Cultures" of Moanan people in Australia and overseas.
- Asserted that there was no democratic process prior to the formulation and legislation of kava laws in the ACT and Australia. Asserted that there was insufficient consultation during the time that restrictions were placed on kava. Members noted that each of the 2003, 2004, 2007 and 2009 considerations of kava included public consultation processes in accordance with requirements specified in the then Therapeutic Goods Regulations 1990.
- Asserted that there was a discrepancy between state (specifically ACT) and Federal restrictions on kava. Claimed that Federal restrictions allowed kava to be used and imported for cultural purposes which was not allowed under ACT legislation.
- Stated that this discrepancy had caused confusion, specifically in relation to the NMF held in the ACT. Asserted that the availability of alcohol at the NMF in contrast to kava had resulted in supporters of the organisation feeling marginalised and isolated.
- Asserted that the following were side-effects of the current kava laws (Members noted that it appears that the following "side-effects" were all enforcement matters):
    - Increase in rate of kava beggars in Australian and Pacific Island international airports seeking to obtain kava from incoming passengers.
    - Increase in rate of illegal importation of kava into Australia at airports and wharfs.

- Increase in rate of black-market supply between the Eastern states and NT and WA.
- Rumoured possibility for "kava boating" to occur between the Pacific Islands and Australia.
- Rumoured possibility of kava cultivation in QLD, NT and WA.
- Possibility of creating Moanan kava fanatics and extremists in Australia.

· Suggested that further case studies on kava and its cultural uses be presented. Also suggested that the Federal and ACT Governments assist the XXXXX to conduct public forums, education campaigns and studies in Moanan languages of the risks and benefits of using kava in traditional ways throughout Australia.

· Suggested that the education campaign described in the Guidelines document be included as part of the regulation of kava. Specifically, the Guidelines document outlined a program of workshops seeking to educate individuals and organisations on traditional and modern Moana culture and its use of kava.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that 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) the toxicity of a substance; and (e) the potential for abuse of a substance.

Members noted that kava importation restrictions/allowances were not dictated by scheduling. Members also noted that although the Customs (Prohibited Imports) Regulations restricted importation of kava quantities exceeding 2 kg, these restrictions are also subject to state and territory-specific controls on kava.

Members discussed whether kava was considered to be captured by the Appendix A general exemption for food. Members noted that although kava was regulated as a food in NZ, no Australian jurisdiction currently considered aqueous kava preparations to be food. Therefore, the current FSANZ Foods Standard 2.6.3 would not be applicable in Australia.

A Member noted that although kava use was associated with raised GGT levels, there was evidence to show this may not translate to increases in liver toxicity. Members discussed the applicability of such findings to communities most likely to use kava preparations. A Member asserted that research suggesting that kava was not associated with liver toxicity was usually conducted in healthy individuals, whereas some communities wishing to access such preparations may suffer from low health standards and poor diet.

Members also discussed what was considered to be "traditional use" of kava preparations. A Member asserted that kava use in accordance with Pacific Islander customs was a more moderate usage pattern with lower risks of harm and the scheduling exemption should be

limited to such circumstances. Other Members disagreed and raised concerns on how such a restriction could be enforced. A Member asserted that a loosening of restrictions on kava would allow at-risk communities access to another substance of abuse and limiting the exemption to traditional use would still result in harm to communities and the overall health system.

A Member recalled the reports of abuse which prompted the original decision to include aqueous kava preparations in Schedule 4. Members noted that these reports of abuse and misuse were not just limited to indigenous communities but also extended to Pacific Islander and other communities. A Member stated that in many of these cases kava abuse was associated with community violence, problems with employment and public health issues. Another Member also raised concerns regarding actions which would allow another drug with a known potential for misuse and abuse onto the market.

A Member strongly asserted, and the Committee generally agreed, that a Commonwealth-wide relaxation of the current restrictions on kava was not appropriate. Members noted that many jurisdictions have mechanisms to allow access to scheduled substances in specific circumstances with approval from an appropriate state or territory authority.

Members also noted claims regarding whether the current restrictions on kava posed an offense against human rights. A Member recalled the 2007 Federal Court case '*Hanes v Human Rights and Equal Opportunity Commission (HREOC) and Commonwealth of Australia*', where HREOC's decision not to inquire into a complaint that the scheduling of a substance constituted a breach of the applicant's human rights was reviewed. The 2007 legal proceedings noted Article 18 of the International Covenant on Civil and Political Rights which states that "*Freedom to manifest one's religion or beliefs may be subject only to such limitations as are prescribed by law and are necessary to protect public safety, order, health or morals…*".

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 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) the toxicity of a substance; and (e) the potential for abuse of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided that the scheduling of *Piper methysticum* (kava) remains unchanged and that kava in aqueous preparations for human non-therapeutic use remains Schedule 4.

2.3 PROPOSED CHANGES TO PART 5 OF THE SUSMP (THE APPENDICES)

2.3.1 ADRENALINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Adrenaline – seeking advice on a proposal to list adrenaline in Appendix H.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the scheduling of adrenaline remains appropriate (i.e. no Appendix H listing).

BACKGROUND

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

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

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

In August 1985, the Schedule 3 and 4 entries for adrenaline were amended to raise the exemption to preparations containing 0.02 per cent. The record of the decision stated that such a low level was not toxic and did not pose a health risk except in diabetics. In February 1999, the NDPSC recommended that New Zealand harmonise with the Australian adrenaline scheduling. New Zealand subsequently agreed with this recommendation.

Adrenaline auto-injectors for use in severe acute allergic reactions have been approved in Australia since August 1993 and are recommended as a part of the action plan for anaphylaxis. Adrenaline 0.15 mg (0.05 per cent) and 0.3 mg (0.1 per cent) auto-injectors are also listed on the Pharmaceutical benefits Scheme (PBS) as an authority required listing for management of acute allergic reactions with anaphylaxis.

In February 2010, the NDPSC considered an application to include adrenaline auto-injectors in Appendix H and agreed that an Appendix H entry was not appropriate. Further details of the NDPSC's February 2010 discussion are provided under the "Initial Submissions" heading below.

XXXXX again submitted an application direct to the Secretariat in support of an Appendix H listing for adrenaline preparations captured by Schedule 3. A delegate agreed that this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

SCHEDULING STATUS

Preparations containing more than 1 per cent adrenaline are captured by Schedule 4. Preparations containing 0.02 to 1 per cent adrenaline are captured by Schedule 3 and preparations containing less than 0.02 per cent adrenaline are unscheduled.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX requested an Appendix H listing for adrenaline auto-injector preparations. The Australian Register of Therapeutic Goods (ARTG) currently lists two types of auto-injector preparations containing 0.15 mg (0.05 per cent) and 0.3 mg (0.1 per cent) of adrenaline for the emergency treatment of acute severe allergic reactions.

The application made a number of overall points, as summarised below:

- Stated that allergy is a chronic condition requiring ongoing management.
- Stated that in recognition of the benefits of early treatment of emerging severe allergic reactions, adrenaline auto-injectors have been included in Schedule 3 to allow pharmacists to dispense in emergency situations.
- Asserted that effective delivery of adrenaline from an auto-injector required consistent training in the devices' use. Stated that an Appendix H listing of the adrenaline auto-injectors was sought to permit direct provision of the company's training materials to workplaces to inform and instruct staff in the effective and appropriate delivery of adrenaline in emergency situations. Argued that while information can be provided on auto-injector use to health care professionals, the applicant is currently prohibited from providing such information to other persons.
- Asserted that this provision of information and education could also emphasise the importance of ongoing re-familiarisation of patients (and their carers) with the use of their auto-injector device.
- Argued that patients and their carers were instructed in the recognition of symptoms and the use of adrenaline auto-injectors. However for motivated members of the general population, although there were many internet sources of information

concerning the recognition of symptoms of anaphylaxis, studies have shown that this was not sufficient for reliable performance in using auto-injectors and further educational effort was required.

- Stated that compliance with the Therapeutic Goods Advisory Code (TGAC) was monitored by the Australian Self Medication Industry (ASMI) and as such, any proposed materials were subject to independent review. ASMI also acts as an arbitrating body when complaints are made.
- Also sought to address some of the concerns raised by the NDPSC in their consideration of the Appendix H entry in February 2010.

The application made a number of points against Section 52E criteria, as summarised below:

(a) Risks and benefits

- Asserted that early adrenaline administration when a severe allergic reaction was suspected was generally accepted as improving the outcome for allergic individuals. Reviews of near fatal cases have shown the timely administration of adrenaline to reduce the need for hospitalisation. Fatalities were associated with the lack, or late administration, of adrenaline.
- Noted a 2005 study reporting that all fatal events occurred outside the home and all non fatal events occurred within the home, suggesting the availability of adrenaline for self administration and the ability to effectively use the device was maximised in the home.
- Noted that the Australasian Society of Clinical Immunology and Allergy (ASCIA) recommend a management plan for patients at risk of hypersensitivity reactions which included specialist assessment, the availability of adrenaline auto-injectors for the management of acute episodes and ongoing monitoring of the patient. ASCIA had also recognised the need for training in the use of the auto-injectors and have available on their website training modules which encompass device use for schools and health-care professionals.
- Asserted that the proposed benefits of an Appendix H listing would allow provision of information on auto-injector use by the applicant to responsible staff in the workplaces who are often not health care professionals. Stated that the training would also cover the recognition of appropriate circumstances to use an auto-injector.
- Argued that while the risk of misdiagnosis of an emerging serious allergic reaction was possible, if individuals, their carers and other responsible adults were well trained to recognise such symptoms, there should be no additional concern.
- Asserted that given the single low dose of adrenaline administered and its short duration of action, the Consumer Medicine Information (CMI) stated that there were no medical circumstances where a single dose of adrenaline (0.15 mg or 0.3 mg) should not be administered to anyone considered to need it.

(b) Purpose and extent of use

- Asserted that the extent of use for adrenaline auto-injectors was not known as it was dispensed in case of need for emergency treatment (and thus all supplied meds may not be used). Therefore the submission estimated its potential use based on the reported hospital admission data for severe allergic or anaphylactic reactions.
- Stated that in 2004/5, approximately 5000 patients out of a population estimate of 20.7 million in Australia were reported to have been admitted for severe allergic or anaphylactic reactions. Based on this estimate suggested that with an increased population of 22.6 million in 2011, the incidence of hospital admissions for allergic reactions would increase to at least 5460 cases.

(c) Toxicity

- Stated that the risks of auto-injectors fell into three categories:
  - risk to the patient from ineffective dose;
  - risk to the carer (or patient) from incorrect use (injection site or technique); and
  - risk to the patient of a possible adverse event to the medicine.
- Asserted that the safety of adrenaline auto-injectors had been demonstrated by the small number of adverse events (AEs) reported to the TGA's Office of Product Review (formerly ADRAC). Since 1993, a total of 16 AEs involving the applicant's brand of auto-injectors: 31 per cent were a result of ineffective delivery, 25 per cent were associated with failing to deliver the dose, 25 per cent reported administration errors and 19 per cent adverse events associated with treatment (including: one urticarial rash, one possible drug interaction resulting in Tako-Tsubo syndrome and one fatal clostridial infection).
- Stated that since December 2008, most AEs reported to the applicant were associated with administration errors (51 per cent), in addition 17 per cent of the events were reported to be device failure and 14 per cent lack of efficacy. AEs to adrenaline administration totalled 14 per cent and including: hospitalisation, cardiomyopathy, gas gangrene and bruising. Stated that upon investigation, the device failures were mostly found to result from user error or misunderstanding of device use.
- Noted that while the data were limited, the predominant concern for safety was the risk to the patient of ineffective delivery of the drug in emergency situations.
- Stated that needle stick injuries of the fingers (or thumb in the above cases) appeared to be the most frequent administration errors, usually resulting in localised ischaemia.
- Asserted that safety when adrenaline was administered in an inappropriate situation was a consequence of the device being a single use, low dose presentation. This resulted in limited toxicity after which the patients recover. The rapid elimination of adrenaline (half life of approximately 5 to 10 minutes) was also likely to contribute to safety.

- Noted that adrenaline was contra-indicated in narrow angle glaucoma, shock, cardiac dilation and coronary insufficiency, but asserted that these contraindications were relative as this product was intended for use in life-threatening emergencies.

(d) Dosage, formulation

- Noted that two auto-injectors under the brand name XXXXX were currently available, with each auto-injector also containing 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite:
  - Auto-injector delivering 0.3 mg adrenaline in 2 mL as a single dose, intended for the treatment of patients weighing over 30 kg.
  - Auto-injector delivering 0.15 mg adrenaline in 2 mL as a single dose, intended for the treatment of children weighing under 30 kg.
- XXXXX

(e) Potential for abuse

- Stated that although adrenaline was not a substance of abuse, there was a potential for inappropriate use given the need to recognise emergent symptoms of severe allergic reactions. However, asserted that an Appendix H listing was unlikely to increase the misuse of auto-injectors by non-health professionals.
- Stated that there were significant costs for purchasing the product outside of PBS subsidy. Stated that while Schedule 3 listing allowed dispensing of the auto-injector by a pharmacist, to obtain the PBS subsidised supply the patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with, an appropriate medical professional or have been discharged from hospital or an emergency department after treatment with adrenaline for acute allergic reaction with anaphylaxis.
- Noted that alternatively, auto-injectors were available on authority for continuing supply for anticipated emergency treatment of acute allergic reactions with anaphylaxis, where the patient had previously been issued with an authority prescription for the product.
- Asserted that patients who suspected they had an allergy, not requiring immediate treatment and without a prescription, were unlikely to be provided with an auto-injector given the proposed Appendix H wording 'for the emergency treatment of severe allergic reactions' and the requirement for the pharmacist to be involved in supply.
- Noted that auto-injector intramuscular injection was painful and the side effects of adrenaline were unpleasant.

(f) Other matters

- Asserted that the current understanding of auto-injector use in individuals outside the patient and their immediate carer may be deficient.

- Cited a study of Sydney preschools which found that the majority of child care workers could not demonstrate the auto-injector correctly and that a similar study in South Australia had come to the same conclusion. Asserted that some prescribers were not always able to demonstrate or effectively use an auto-injector.
- Noted that a survey of 101 families of food allergic children (most of whom had an auto-injector prescribed) found that only 71 per cent of the study participants carried their auto-injector regularly, and among those, 10 per cent were found to have carried a device that had passed its expiry date. The study also found that only 32 per cent of participants correctly demonstrated use of their device and only 18 per cent of the 29 paediatricians in this study were able to correctly use the device.
- Asserted that although ASCIA and patient groups were actively disseminating information for the use of auto-injector devices, given the increasing prevalence of and enlarging population of individuals at risk, reaching such a broad population for face to face education may be limited. Asserted that although motivated personnel at schools and other work places may be able to gain some information via the internet they were likely to lack regular direct training in device use and symptom recognition.
- Noted a recent UK study which showed that parents who sought additional information from a national self-help allergy organisation were 4-6 times more likely to be competent in the use of auto-injectors.

Evaluation Report

The evaluator did not make an explicit recommendation as to whether an Appendix H entry would be appropriate for adrenaline auto-injectors. However, the evaluator made a number of points, as summarised below:

- Stated that the application had appropriately argued that there were benefits of early, effective treatment of patients suffering acute, severe allergic reactions.
- In relation to the studies provided in support of the application, stated that although some of these were of small sample size and retrospectively conducted, it was not too contentious to accept that timely recognition of an allergic episode and subsequent effective delivery of treatment would be important.
- Noted the application's data regarding the extent of use of adrenaline auto-injectors and asserted that it was likely that the numbers provided would be an underestimate of the actual use in the community.
- Noted the application's argument that as the prevalence of food allergies in children and insect stings in adults have increased in Australia, that there would be an increased administration of adrenaline during school hours and/or at the workplace and care facilities. Noted that it was argued that teenagers may neglect to carry their auto-injector for a variety of social reasons and that some patients may be disinclined to inflict a deep intramuscular injection on themselves. Based on these, the

application then argued that there were occasions where a responsible adult other than the individual or their primary carer would need to administer adrenaline.

- Stated that it also appeared reasonable that there were likely to be occasions where a responsible adult other than the individual or their primary carer would need to administer adrenaline in an emergency. However, it remained uncertain how often this administration was likely to occur (some small studies were cited by the application, but did not provide population data on the likelihood of this administration by a responsible person). Noted that with the exception of drug-induced anaphylaxis deaths, despite increasing anaphylaxis prevalence, anaphylaxis mortality rates in Australia have remained low and stable.
- Stated that it was uncertain whether the administration of adrenaline by a lay person would require the patient to be carrying his/her adrenaline, or whether it will be assumed that the lay person would keep a supply.
- Stated that while the application's claims of a potential need for education would appear to be generally appropriate, the risk benefit assessment would rely largely on the adequacy of the training to be provided as a result of an Appendix H listing. Stated that the application had appropriately acknowledged that there was a risk for the misdiagnosis of an emerging serious allergic reaction and such risk could only be mitigated if the individuals were well trained, thus recognising the quality of the training to be important.
- In relation to the UK study showing that parents who sought additional information were more likely to be competent in the use of auto-injectors, stated that this study was conducted specifically in parents of children who suffer from allergies and thus the conclusions of the study may not apply to lay persons who were not directly related to the child. However, these lay persons would be the target audience for the proposed advertising by the applicant. Also noted that the study's main conclusion was that more education should be given to parents at the time of adrenaline prescribing.
- Raised concern that some of the AE data reported in the application only reported percentages and not discrete number of events. However, agreed that when administered appropriately, auto-injectors had limited toxicity and that most reports of adverse reactions appeared to be associated with inadequate administration technique. Stated that the designation of the auto-injector as a Schedule 3 item would also have required the demonstration of its relative safety.
- Agreed with the application that in most cases, severe allergies would be diagnosed by a specialist who would then formulate an action plan for the patient which may include an adrenaline auto-injector. Noted that although there may be occasions where a patient with a diagnosis of severe allergy may require a responsible personal to assist with the administration of their prescribed adrenaline, it would be considered highly inappropriate for any non-medically trained persons in work places to diagnose severe allergy in patients.

- Asserted that the NDPSC's concern regarding an increase in the misuse of auto injectors by non-health professionals had not been adequately addressed in the application. Stated that the majority of the application's arguments related to the supply of auto-injectors via the PBS, which was more restrictive than supply as Schedule 3. Stated that while it was appropriately argued that the supply of adrenaline via the PBS would limit inappropriate supply to patients, such arguments would not generally apply to the broader community. It is envisaged that the community would mostly be obtaining the auto-injector via a pharmacy (without a script), as they would not be able to obtain a prescription from a doctor if they did not suffer from severe allergies themselves. Thus it was likely that advertising to the community would encourage the storage of an adrenaline auto-injector for emergencies resulting in an increase in demand in pharmacies.
- In relation to the role of pharmacy assistants in the supply of auto-injectors, stated that such a role would appear to be minimal. As adrenaline auto-injectors are listed as Schedule 3 medicines, supply would be restricted to a pharmacist who could assess the appropriateness of use and provide effective counselling. Thus it is envisaged that any inquiries regarding the auto-injector would also be dealt with by a registered pharmacist and not by the pharmacy assistant.
- Stated that the ACMS and delegate would need to take into account the potential public benefit versus any risks associated with potential inappropriate use by the community as a result of the advertising. Asserted that although it appears appropriate that education of patients, carers and responsible persons would be of public benefit, the benefit was heavily dependent on the quality of such proposed training, the likelihood that a responsible person would need to administer adrenaline and whether inappropriate advertising was likely and how such advertising would ensure that quality training was delivered. Asserted that the application had not fully addressed these issues.
- Asserted that, as the Committee had not yet seen any proposed advertising material for the purposes of education, the full impact of any such messages could not be fully assessed. Thus the possibility that these materials may generate inappropriate use could not be excluded.

Applicant's Response to the Evaluation Report

XXXXX response addressed matters raised by the evaluator, summarised as follows:

- Overall, asserted that concerns regarding inappropriate requests to pharmacists for the auto-injector have been raised but the proposed targeting of workplaces would limit this prospect. Asserted that concerns raised by the evaluator would be addressed if the Appendix H entry for adrenaline would be specifically limited to "*for the emergency treatment of acute anaphylaxis (acute severe allergic reactions) due to insect stings or bites, foods, drugs or other allergens - which may occur in places of business, education or public venues*".

- In relation to the evaluator's statements on low anaphylaxis mortality rates in Australia, asserted that quotation of mortality rates disguised the increase in absolute numbers of patients dying of severe allergy in proportion to the population. Stated that adrenaline was also intended to be used to reduce the need for hospital admission, not only the risk of death, and that this need was increasing.
- Asserted that the increased rates of hospitalisation associated with an anaphylactic event could be interpreted as arising from increased severity of events, potentially due to ineffective or lack of use of adrenaline injectors. Stated that current training supported by the applicant could not effectively address this deficiency.
- Stated that they could not locate statistics concerning the rate of severe allergic reaction events not resulting in hospitalisation, but that these rates may be assumed to be increasing at least as rapidly as for events requiring hospital treatment.
- Stated that it was not intended that the general public be equipped at all times with an adrenaline auto-injector in case they come across someone experiencing an anaphylactic event. It was considered more likely that schools and workplaces should have an auto-injector available for use, since it was more likely that events would occur in these environments.
- In relation to the evaluator's statements on the adequacy of the training/advertising to be provided through Appendix H, asserted that the applicant has close relationships with experts in the area of anaphylaxis and currently provides training materials for the use of health care professionals when counselling patients and their carers. Stated that the current training materials were developed in consultation with a number of these experts and would continue to be developed in this manner. Asserted that all materials intended for use with patients were required to be reviewed and approved by ASMI prior to distribution.
- In relation to the evaluator's comment on advertising encouraging the community into inappropriately purchasing auto-injectors, asserted that there was a significant cost disincentive for the general public to obtain an auto-injector from a pharmacy which would self limit requests. Reasserted that given the requirement for the involvement of a pharmacist, inappropriate use would be limited. Stated that similar requirements apply to many antifungal, anti-inflammatory and antihistamine products which are advertised direct to the public.
- In relation to the evaluator's comment on the UK study showing that parents who sought additional information were more likely to be competent in the use of auto-injectors, asserted that most parents of children with a history of anaphylaxis, or at high risk of an anaphylactic event, were also 'lay persons' with no special knowledge of health and medicines prior to their initial counselling by the treating physician. Asserted that there could only be benefit in providing to carers and patients the same information and training materials suitable for naive lay persons.
- In relation to the evaluator's comment on the impact of messages contained in the advertising, stated that the submission of training material was not required as part of

the review process and could not in any case be all-encompassing, given the potential for changes in the management of allergic reactions over time.

- In relation to the evaluator's comment on non-medically trained personnel diagnosing severe allergy stated that it was not intended that a lay person should be trained to diagnose patients with severe allergy. Asserted that instead they must be able to recognize the symptoms of a severe allergic reaction if adrenaline was to be administered effectively in a timely manner. In most cases the patient would be able to identify themselves as an allergy sufferer and the likely allergen exposure. Stated that this was no different from a parent or carer being required to do the same.

NDPSC February 2010 discussion

The NDPSC made a number of points in their discussion at the February 2010 meeting, as summarised below:

- The NDPSC agreed that the education of patients and carers in the effective use of auto-injectors was important. However, less clear was the need to allow brand name advertising through an Appendix H listing to achieve this education. An NDPSC Member asserted that education was usually provided by the doctor when the auto-injector was first prescribed and further information was also available from the dispensing pharmacist. Other Members asserted that while the public was not generally well educated on issues relating to acute anaphylactic reactions nor trained to administer adrenaline; those affected were usually highly educated regarding the issues (particularly parents).
- The NDPSC also noted that there were already a number of avenues for adrenaline auto-injector training. While there were restrictions regarding branded advertising, NDPSC Members noted that education groups were allowed to provide information on adrenaline auto-injectors, independent of brand. A Member particularly noted the roll-out of a substantial Western Australian education program on this issue. Another Member noted that a number of effective programs were supported by various jurisdictions and asserted that the applicant's argument regarding the need for Appendix H listing to address an unmet education need was overstated.
- Several Members also supported concerns raised in some pre-meeting comments that advertising of auto-injectors may target or pressure the general community into purchasing auto-injectors without need and cause an influx of inappropriate requests to pharmacists. It was asserted that, with the availability of new types of auto-injectors, advertising had the potential to cause confusion for patients regarding the different methods of administration.
- A Member also asserted that it should be kept in mind that auto-injectors were included in Schedule 3 to facilitate emergency access for a specific group of people rather than the usual purpose of the majority of Schedule 3 listings i.e. to provide the community with access to a beneficial therapeutic option which required professional

advice but not a prescription. The Member was concerned that advertising could undermine this distinction.

October 2011 Pre-meeting Submissions

Five pre-meeting submissions were received. XXXXX did not support inclusion of adrenaline in Appendix H.

XXXXX (allergy specialist) supported the availability of wider awareness of the appropriate use of auto-injectors but not direct consumer promotion. XXXXX supported the need for education, but raised concerns regarding direct to consumer promotion.

XXXXX supported listing of adrenaline in Appendix H to facilitate awareness, education and training of consumers and carers.

The submissions made a number of points, as summarised below:

XXXXX

- Acknowledged that responsible advertising of Schedule 3 products may have some public benefit by raising consumer awareness of health conditions and prompting health professional intervention. However, raised concerns about consumers requesting products based on an advertisement.
- Stated that with Schedule 3 medicines, it was the pharmacist's responsibility to assess that the product was safe and suitable for the patient. Asserted that this could be difficult when the customer had made up their mind and believed that they knew best because of the limited, sometimes exaggerated information provided in an advertisement.
- Stated that while adrenaline auto-injectors were easy to use, training/counselling was necessary. Stated that information and training for both brands of auto-injectors currently available in Australia was available online (Epipen® - www.epiclub.com.au, Anapen® - www.anapen.com.au).
- Stated that patients who would benefit from having access to adrenaline auto-injectors were best identified through health care professional intervention rather than by advertising campaigns.
- Asserted that in the event that adrenaline was included in Appendix H, pharmacists would benefit from support materials to filter inappropriate requests and ensure legitimate users were under medical supervision.
- Stated that it may not be appropriate for a medicine subsidised under the PBS to be advertised directly to consumers. Requested clarification on this point.

Evidence of advertising need

- Stated that due to PBS restrictions and costs, it was reasonable to expect auto-injectors to be initiated by a specialist. Stated that prescribers and pharmacists were

well placed to identify patients at particular risk of anaphylactic reactions for referral to a specialist.

- Noted that restricted promotion of adrenaline auto-injectors through consumer support groups occurs in New Zealand for relevant conditions such as asthma. Stated that while there may be benefits to having limited promotion such as this, Appendix H does not include such restrictions and it would therefore be possible for sponsors to initiate more extensive campaigns.

Risk of inappropriate product requests

- Raised concerns that direct to consumer advertising may prompt people with non-anaphylactic allergies to seek an adrenaline auto-injector. Asserted that consumers had a poor understanding of allergies, as demonstrated when health professionals question them on medicine allergies. Stated that it was not uncommon for a consumer to report that they had a drug allergy when experiencing drug sensitivity or an adverse drug reaction.
- Raised concerns that strategic advertising could promote an adrenaline auto-injector in such a way that pharmacists would need to spend significant time and effort in assessing the appropriateness of the request.
- Questioned whether advertising would succeed in identifying a greater number of patients who would benefit from having access to adrenaline auto-injectors for emergency use or whether it would more likely prompt inappropriate requests.

XXXXX

- Asserted that direct consumer promotion of adrenaline auto-injectors was medically inappropriate. Stated that current access to auto-injectors was appropriate since the devices could be purchased over the counter without prescription if required. Stated that direct consumer promotion increased the risk of inappropriate purchase without medical advice and thus potentially altered the risk/benefit ratio.
- Stated that ASCIA had developed prescribing guidelines for adrenaline auto-injectors to assist with the determination by medical professionals of level of risk of anaphylaxis and therefore the requirement for an adrenaline auto-injector. Asserted that direct consumer promotion may result in the purchase of adrenaline auto-injectors by patients who do not normally require these devices (e.g. individuals with a family history of anaphylaxis, allergy or asthma, but no personal history of anaphylaxis).
- Stated that the purchase of adrenaline auto-injectors which were not considered to be medically indicated may result in upwards pressure on PBS costs by demands by patients for renewal using PBS authority subsidized prescriptions.
- Stated that the dose recommendations on the Product Information (PI) leaflet differed to that recommended by ASCIA. Members noted that ASCIA had clarified that this dose difference was in relation to the weight of the patient – i.e. ASCIA

recommended the lower concentration auto-injector (0.15 mg) for use in patients up to 20 kg, not 30 kg as set out in the PI.

- Stated that ASCIA dose recommendations were based on consensus and standard practice by ASCIA members and published in the Australian Medicines Handbook and the National Prescribing Service information on adrenaline auto-injectors. Asserted that direct consumer promotion to consumers may result in confusion in terms of which dose device (0.15 mg or 0.30 mg) was appropriate. Further stated that ASCIA dose recommendations did not support adrenaline auto-injector provision to infants unless determined as necessary by a clinical immunology/allergy specialist.
- Asserted that through direct consumer promotion the opportunity for patient education on avoidance of anaphylactic triggers and training in appropriate device use would be lost. Stated that while pharmacists play a role in patient education, medical advice and training of patients was an essential part of anaphylaxis management. Asserted that this was even more important as two very different devices were currently available on the market.
- Asserted that advertising may favour one product over another and would therefore present a biased viewpoint to individuals who were not medically trained.
- Stated that ASCIA, in collaboration with Anaphylaxis Australia and Allergy New Zealand, were developing e-training programs to increase community awareness of anaphylaxis through high quality anaphylaxis training and resources. Stated that the e-training programs for schools and childcare have educated over 11,500 individuals since it was launched in March 2010 and it was the preferred anaphylaxis e-training course in NSW, WA and QLD and the only anaphylaxis management training available in some regions in Australia.
- Stated that ASCIA were currently adapting anaphylaxis e-training for schools and childcare into an anaphylaxis e-training course for the community, which would address first aid issues and would be targeted at the general public. Asserted that commercial promotion of adrenaline auto-injectors to consumers had the potential to undermine the educational programmes developed.

XXXXX ***(allergy specialist)***

- Stated that it would be beneficial if training materials could be created for awareness of auto-injectors in places such as public event areas, workplaces and schools.
- Stated that allergies were increasing in Australia and death from severe allergy was more likely to occur with failure to provide early and appropriate care. Asserted that there was a limitation of access to experts in Australia for appropriate training in anaphylaxis. Stated that the proposed amendment may help in this regard.

XXXXX

- Stated that there was some merit in companies having the ability to communicate directly with individuals (e.g. pharmacy assistants, medical practice workers). However, raised concerns about companies communicating with the general public where there was no health professional (e.g. pharmacist or doctor) on location.
- Stated that awareness of allergy and anaphylaxis had improved in the general community, however asserted that there was a continual struggle with dissemination of accurate information on allergy and the risk of anaphylaxis.
- Asserted that there was confusion within the community about allergy and risk of anaphylaxis and it was essential that individuals with allergy symptoms were appropriately diagnosed by an immunology/allergy specialist.
- Raised concerns that direct consumer promotion could result in individuals purchasing an adrenaline auto-injector when they do not require one. Stated that there was still limited understanding of anaphylaxis within the community and it was not unreasonable for individuals to purchase an auto-injector for themselves or their child without medical confirmation of such a need.
- Also reiterated an earlier submission's point that the ASCIA prescribing guidelines differed from the PI and that auto-injectors were not recommended for children under a certain age. Asserted that individuals encouraged to purchase an adrenaline auto-injector may purchase the wrong dose device and not have the required documentation signed by their doctor (Action Plan for Anaphylaxis – an individualised emergency response plan).
- Raised concerns regarding the purchase of an auto-injector with no/incorrect education on how to avoid allergic reactions and when to use the device.
- Asserted that direct consumer promotion could lead to the presentation of biased information by the pharmaceutical companies promoting the device.

XXXXX

- Stated that given the purpose of use of adrenaline auto-injector preparations (i.e. emergency treatment of acute severe allergic reactions), permitting direct communication with consumers would be likely to assist with:
  - raising broader awareness regarding the need for, and availability of, treatment to increase understanding for members of the public if they encounter such emergencies;
  - developing education and training which was uniform across organisations and locations;
  - delivering up-to-date education which could be tailored for the device and the audience; and
  - making education and training accessible on a regular basis (rather than a one-off or ad hoc exercise) so that potential users, carers and health professionals were

better prepared and more confident in managing highly stressful emergency situations.

- Noted that the rationale behind the previous request for Appendix H listing focussed on the ability to deliver education and training to non-healthcare professionals. Noted that while Appendix H listing allowed brand advertising, also asserted that the risk of misuse or inappropriate requests as a result of brand advertising was low.
- Acknowledged concerns previously raised regarding use of brand advertising to educate consumers and carers. However, asserted that, on balance, the inclusion of adrenaline in Appendix H had the potential to deliver benefits.
- Noted the importance of ensuring that messages to consumers were conveyed in a manner that highlighted a product's purpose of use and that they did not inadvertently send confused or unintended messages. Expressed confidence that this would be managed through the application of the Therapeutic Goods Advertising Code.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (f) other matters considered necessary to protect public health.

Members discussed the risks and benefits of inclusion of adrenaline auto-injectors in Appendix H. A Member asserted, and the Committee generally agreed, that direct-to-consumer advertising promoting sales of adrenaline auto-injectors was not appropriate. A Member suggested limiting the Appendix H entry to only allow specific types of promotion (e.g. community training) and to exclude media advertising. A Member asserted this was appropriate as the mode of use of the different brands varied; it was therefore important to be able to use the brand names in any training programs. However, another Member noted that inclusion in Appendix H did not control the type of advertising used to promote a substance and asserted that inclusion of a substance in Appendix H effectively gave companies 'carte blanche' on methods of direct-to-consumer promotion and that a simulated device could be used in training programs. Another Member asserted that the content of advertising was subjected to significant consideration against TGAC requirements prior to being approved. However, another Member raised concerns regarding common community misperception of risks of anaphylaxis vs less serious but more common food sensitivities and the potential effect of widespread advertising on the public. Several Members therefore asserted that allowing brand advertising could draw on these community misperceptions and lead to an increase in inappropriate purchasing and possession of these devices.

Members noted current efforts by ASCIA and Anaphylaxis Australia on increasing community awareness of anaphylaxis and training in the use of auto-injectors. Members also noted current work underway in several jurisdictions seeking to address these issues in response to community concerns. A Member asserted that training on use of adrenaline auto-injectors would be best left to organisations without a commercial

interest in the product. Another Member also noted that information training could currently be run by public health groups with input from sponsor companies. Members generally agreed that an Appendix H entry for adrenaline auto-injectors was not appropriate.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendation of the ACMS was clear and appropriately supported. The delegate agreed with the recommendation.

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 considered necessary to protect public health.

DELEGATE'S INTERIM DECISION

The delegate decided that the scheduling of adrenaline remains appropriate (i.e. no Appendix H listing).

2.3.2 FINGOLIMOD

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Fingolimod – seeking advice on a proposal to include fingolimod in Appendix L with a requirement for labelling with warning statement 76 "*Do not become pregnant during use or within [2] months of stopping treatment.*"

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that fingolimod be included in Appendix L with a requirement for labelling with warning statement 76.

The Committee also recommended an implementation date of no more than six months after the delegate's final decision (i.e. 1 May 2012).

BACKGROUND

Fingolimod is an immunomodulator indicated for the treatment of Multiple Sclerosis (MS). 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.

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.

In June 2011, a delegate made a final delegate-only decision to include fingolimod in Schedule 4. The delegate noted that fingolimod was 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."*

The delegate decided to refer a proposed Appendix L entry for fingolimod to the ACMS for advice due to the potential for adverse pregnancy effects associated with fingolimod.

SCHEDULING STATUS

Currently, fingolimod is listed in Schedule 4. New Zealand restrictions for fingolimod are equivalent.

INITIAL SUBMISSIONS

ACPM Consideration

In December 2010, the Advisory Committee on Prescription Medicines (ACPM) considered a submission from XXXXX to register XXXXX containing the new chemical entity, fingolimod hydrochloride XXXXX.

XXXXX

The ACPM minutes made a number of additional points, as summarised below. The ACPM Minutes, however, provided limited information on the use of fingolimod in pregnancy:

- The safety and efficacy of fingolimod beyond 2 years were unknown.
- Recommended that specific conditions of registration include routine pharmacovigilance, monitoring of suicide rate in patients and a pregnancy registry.
- Fingolimod was initially developed for use in combination with cyclosporine A and corticosteroids for the prevention of acute rejection after renal transplantation, but that clinical program was discontinued because the addition of fingolimod did not result in improved efficacy. It was subsequently developed for use in patients with MS.
- Fingolimod was approved in the USA in September 2010. An earlier submission was placed on a full clinical hold because of several safety concerns until the FDA and the sponsor reached agreement about safety monitoring in MS studies in May 2006. An application for approval has also been submitted to the EU.
- Given that initial development of fingolimod was for prevention of rejection of renal transplant, subjects in the clinical studies were mostly healthy volunteers or renal

transplant patients. Additional data were subsequently obtained from safety and efficacy studies in MS patients.

- The 3 major adverse effects of fingolimod were decrease in peripheral lymphocyte count, decrease in heart rate and increase in airway resistance.
- Toxicity was dose related. Toxicological issues identified included increased risk of:
  - Infection;
  - Lymphomas;
  - Sinus arrhythmias, bradycardia and dyspnoea at treatment initiation;
  - Pneumonia, congestion and bronchial collagenisation with long term scarring and subsequent deterioration of pulmonary function; and
  - Adverse fetal effects during pregnancy.

According to the Martindale monograph for fingolimod, there were no human data for use of fingolimod in pregnancy. However, developmental toxicity has been shown in rats and rabbits, and since the sphingosine 1-phosphate receptor is involved in vascular formation during embryogenesis, US licensed product information recommends that fingolimod should only be used during pregnancy if the potential benefit outweighs potential risks to the fetus. These risks may persist for 2 months after stopping treatment. Additionally, women of child-bearing potential are advised to use effective contraception during fingolimod treatment and for 2 months after treatment stops.

October 2011 Pre-meeting Submissions

No pre-meeting submissions were received on this item.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* were (a) the risks and benefits; (b) the purposes and extent of use; (c) toxicity; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

Members noted there was generally a lack of data on the effects of fingolimod in human pregnancy. The data available, however, showed that fingolimod had caused developmental problems in animals. When fingolimod was administered to rats during organogenesis, the most common malformation was cardiovascular abnormalities. Rats also showed an increase in skeletal variations and reduced perinatal survival.

A Member noted that the European Medicines Agency had made available a public assessment of fingolimod. This assessment reported thirteen pregnancies in women using this drug, with one congenital abnormality that had led to an abortion. As a result, the agency had prepared a doctor's checklist for use when prescribing the drug. This checklist included 2 points where the prescribing doctor must advise potential mothers to

avoid pregnancy and use effective contraception while taking fingolimod and in the 2 months after treatment ends.

The Committee agreed that an Appendix L entry would be appropriate. Members agreed that the proposed warning statement was consistent with the Consumer Medicines Information and requiring a warning statement on the dispensing label would ensure that consumers would always be warned regarding the risks associated with taking fingolimod in pregnancy.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendation of the ACMS was clear and appropriately supported. The delegate agreed with the recommendation.

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

DELEGATE'S INTERIM DECISION

The delegate decided to include fingolimod in Appendix L with a requirement for labelling with warning statement 76. The delegate decided that an implementation date of 1 May 2012 was appropriate (i.e. three months after publication of the final decision).

Appendix L – New entry

Column 1	**Column 2**
Substance	**Warning Statement**
Fingolimod.	76