Australian Government

Department of Health and Ageing

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

SEPTEMBER 2011

Delegates' final decisions on scheduling matters:

- Initially referred to the June 2011 meeting of the Advisory Committee on Chemicals Scheduling (ACCS) [**ACCS#2**];
- Initially referred to the June 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS) [**ACMS#3**]; or
- Considered as delegate-only matters i.e. were not referred to an advisory committee.

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

A delegate of the Secretary to the Department of Health and Ageing hereby gives notice of delegates' final decisions for amending the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* – SUSMP) under subsections 42ZCZS and 42ZCZX of the Regulations. This notice also provides the reasons for each decision and the date of effect of the decision. Edited versions of further submissions on interim decisions for matters referred to ACCS#2, or ACMS#3 are also available at www.tga.gov.au/industry/scheduling-submissions.htm.

Matters referred to ACCS#2 and ACMS#3

Delegates' interim decisions on recommendations by ACCS#2 and ACMS#3 were published on 24 August 2011, accessible at www.tga.gov.au/industry/scheduling-decisions-interim.htm. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions (published 13 April 2011, accessible at www.tga.gov.au/newsroom/consult-scheduling-acmcs.htm).

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

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

Matters not referred to an advisory committee

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

Implementation

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

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GLOSSARY

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

CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments
CRC	Child-Resistant Closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority (NZ)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
HCN	Health Communication Network
HCP	Health Care Provider
INN	International Non-proprietary Name
ISO	International Standards Organization

LC_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MCC	Medicines Classification Committee (NZ)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-Prescription Medicines [ACNPM])
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (was Office of Prescription and Non-prescription Medicines)
OOS	Out of Session

OTC	Over-the-Counter
PACIA	Plastics And Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted Flow Insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee

TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working Party
WS	Warning statement

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

1. MATTERS INITIALLY REFERRED TO ACCS#2 – JUNE 2011

1.1 MESOTRIONE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Mesotrione – proposal to include mesotrione in Schedule 5 or Schedule 6.

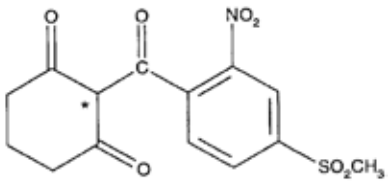
EXPERT ADVISORY COMMITTEE RECOMMENDATION

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

BACKGROUND

Mesotrione is a β-triketone inhibitor of 4-hydroxyphenyl pyruvate dioxygenase (HPPD) activity and belongs to the group of benzoylcyclohexanedione herbicides. Mesotrione has herbicidal activity against broadleaf weeds. It disrupts the carotenoid biosynthesis in the chlorophyll pathway of sensitive plants and this results in a bleaching effect.

The IUPAC name for mesotrione is 2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione and the structure is:



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

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

SCHEDULING STATUS

Mesotrione is not currently specifically scheduled. It appears that there is no current entry that would capture it as a derivative, nor would any group entry.

INITIAL SUBMISSIONS

Applicant's submission

The evaluator found that, based on the toxicity profile (the observed slight eye irritation XXXXX) of mesotrione, it would be appropriate to include this substance in Schedule 5 with no cut-off. Members, however, noted that the delegate's proposal differed from the evaluator's recommendation as the information on developmental toxicity XXXXX may have been of concern and could potentially have warranted a Schedule 6 listing.

Other evaluator conclusions included:

- There were no objections on human health grounds to the approval of mesotrione TGAC XXXXX.
- The ADI for mesotrione was established at 0.01 mg/kg bw/d based on a NOEL of 1.8 mg/kg bw/d in a XXXXX-week dietary study in XXXXX, using a refined 200-fold safety factor consisting of safety factors of 10 for intraspecies and interspecies variation, and a safety factor of 2 intended for the further protection of children and infants.
- The ARfD for mesotrione was established at 0.1 mg/kg bw/d based on a LOEL of 100 mg/kg bw/d in an oral developmental toxicity study in XXXXX, using a refined 1000-fold safety factor consisting of safety actors of 10 for intraspecies and interspecies variation, and a safety factor of 10 for gaps in the database (i.e. use of a LOEL in the absence of a NOEL).

XXXXX

- XXXXX

Toxicology

Members noted the following toxicology summary for the TGAC mesotrione:

XXXXX

- Mesotrione had low acute oral XXXXX, dermal XXXXX and inhalational toxicity in XXXXX. It was a slight eye irritant but not a skin irritant in XXXXX. Mesotrione was not a skin sensitiser in XXXXX.
- Eye irritation: In a non-irrigated test, minimal corneal opacity and irititis was observed XXXXX post dose only in XXXXX animal. No effects on the cornea or iris were seen in the XXXXX remaining animals. Thus, as these minimal and brief observations were not reproduced in the majority of animals, the evaluator considers that results of the study did not provide robust evidence of a moderate eye irritation potential. Overall, noting that the observed slight conjunctival chemosis was absent in animals by day XXXXX and the observed slight conjunctival redness was only

seen in XXXXX animals at study termination XXXXX, the evaluator considered that the findings supported a slight irritation potential.

- In an acute dermal toxicity study, XXXXX of mesotrione was applied to XXXXX. Transient and slight oedema and erythema was observed in XXXXX. There were no signs of erythema, oedema or any additional signs of irritation seen after XXXXX. The evaluator concluded that mesotrione was non-irritating to XXXXX.
- In repeat dose oral studies, the primary effect was an increase in plasma tyrosine levels, inhibition of liver HPPD activity and increased activity of liver tyrosine aminotransferase leading to ocular effects. XXXXX tended to be less susceptible to the ocular effects than XXXXX. Additionally, the similarities in tyrosine kinetics between human and XXXXX suggests the XXXXX may be a better model than the XXXXX for human risk assessment purposes. Furthermore, available evidence from human cases of hereditary diseases that affect tyrosine metabolism indicated that there is a threshold of plasma tyrosine concentration for ocular effects in humans and in the event of complete inhibition of HPPD, this threshold was unlikely to be exceeded in humans.
- Mesotrione was not considered to be an *in vivo* genotoxicant, carcinogenic in XXXXX, a reproductive toxicant in mice or neurotoxic in XXXXX.

Members noted the following information regarding developmental toxicity effects of mesotrione:

- XXXXX were administered mesotrione orally at XXXXX. Apart from XXXXX of the animals in the XXXXX none of the animals showed significant weight loss or adverse clinical signs prior to aborting their litters.
- The report asserted that while the XXXXX incidence of abortion at XXXXX was at an incidence that can be seen in control groups in studies of this type XXXXX, at XXXXX the possibility of abortion being a treatment-related effect could not be dismissed. To assist in determining the significance of this finding a further study was conducted by the same laboratory using the same strain of XXXXX (from the same source) in which animals were also administered XXXXX of mesotrione by gavage on days XXXXX of gestation. No incidence of abortion was seen at XXXXX in this later study. The findings in this earlier study were not reproducible (i.e. not confirmed). The findings of XXXXX instances of abortion at both XXXXX and XXXXX were likely incidental (i.e. spontaneous) and did not provide robust evidence of a treatment related effect. Pregnancy rates between the control and treated groups were unaffected. No treatment related effect was seen on mean maternal bodyweight. No treatment related effect was seen on the number, growth, sex or survival of the foetus *in utero*.
- A statistically significant increase in the incidence of partially ossified odontoid, 27 pre-sacral vertebrae and 13th extra rib of normal length was seen at XXXXX and greater. While these minor skeletal findings were treatment related, an increase in these common variants alone was not of sufficient severity that mesotrione would be

considered a developmental toxicant. Thus, the NOEL for maternal toxicity was XXXXX, and a NOEL for developmental toxicity could not be established. The LOEL for developmental toxicity was XXXXX based on an increased incidence in minor skeletal variations.

- In another study, pregnant XXXXX were administered mesotrione by gavage XXXXX on days XXXXX of gestation, XXXXX per cent tyrosine in the diet from XXXXX of gestation, XXXXX mesotrione orally by gavage at XXXXX on days XXXXX of gestation along with 1 per cent tyrosine in the diet from days XXXXX of gestation, or control diet throughout the study. No maternal toxicity was seen in XXXXX at XXXXX. However, an increase in the incidence of minor skeletal defects/variations was seen in animals receiving XXXXX. Thus, the maternal NOEL was XXXXX while a NOEL for developmental toxicity was not established XXXXX. The evaluator asserted that while the increase in common minor skeletal variants were treatment related these findings alone did not provide sufficient evidence that justify mesotrione being considered a hazard for developmental toxicity.
- Results from the other dose groups included in this study found that there was evidence of increased incidence of the observed minor skeletal defects/variations associated with increased plasma tyrosine levels. That is, with the exception of incompletely ossified 7th sternebrae, the highest incidence of the observed skeletal findings was seen in animals receiving both tyrosine and mesotrione combined which resulted in the highest plasma tyrosine levels.
- Pregnant XXXXX were administered mesotrione XXXXX from days XXXXX of gestation. No treatment related deaths or clinical signs were observed, and there was no effect of mesotrione administration on maternal body weight, food consumption or microscopic findings post mortem. There was no treatment related effect on the number, growth or survival of the foetuses *in utero*. A treatment related increase was seen in the incidence of minor skeletal defects/variations in animals receiving XXXXX. Thus, the maternal NOEL was XXXXX while the NOEL for developmental toxicity was XXXXX. However, the evaluator asserted that while the increase in common minor skeletal variants are treatment related these findings alone did not provide sufficient evidence that justified mesotrione being considered a hazard for developmental toxicity.

Developmental toxicity – evaluator's conclusion

- In developmental toxicity studies in XXXXX an increased incidence of minor skeletal findings was seen in the absence of maternal toxicity. It was considered that these minor skeletal findings alone did not provide sufficient evidence that justified mesotrione being considered a hazard for developmental toxicity and were unlikely to have serious implications for growth and development in humans.
- The evaluator asserted that the mode of action of mesotrione (inhibition of 4-hydroxyphenol pyruvate dioxygenase activity) was similar to other herbicides such as pyrasulfotole and isoxaflutole which were previously assessed in 2007 and 1997, respectively. Both pyrasulfotole and isoxaflutole, which in developmental studies

also produced minor skeletal variations in the absence of maternal toxicity, are listed in Schedule 5.

- Members noted that in June 2007 the NDPSC noted pyrasulfotole's moderate eye irritant potential and low acute oral, dermal and inhalation toxicity, and decided to include it in Schedule 5. The Committee also noted that developmental studies revealed no teratogenicity, although there was some foetotoxicity (increased skeletal variations) in the absence of maternotoxicity in XXXXX.

- In May 1997 the NDPSC listed isoxaflutole in Schedule 5. The Committee noted that despite the low NOELs XXXXX, isoxaflutole was not a highly toxic compound when ingested for long term. The Committee also noted that there was no increase in mortality in any of the chronic studies, even at doses of XXXXX, there were no significant findings of concern in reproduction and developmental studies and the compound was not a genotoxin.

Hazard Classification for the TGAC

· Mesotrione was listed on Safe Work Australia's (SWA) Hazardous Substances Information System (HSIS) Database with risk and safety phrases to address environmental concerns only. No risk phrases based on health concerns were assigned and on the basis of this evaluation report, the evaluator has agreed with this entry.

Product XXXXX

XXXXX

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

· In a single eye irritation study, XXXXX of the product was instilled into the conjunctival sac of three XXXXX. No effects on the cornea or iris were seen in any animal. Conjunctiva redness was seen in XXXXX at XXXXX h, XXXXX at XXXXX h, XXXXX at XXXXX h and was absent in all animals at XXXXX h. Slight conjunctival discharge was seen in XXXXX at XXXXX h only. There were no reports of chemosis. The evaluator concluded that the product formulation was slight eye irritant to XXXXX.

· In a single skin irritation study, XXXXX mL of the product was applied to XXXXX. Slight to well defined erythema was observed in XXXXX animals up to day 2. On day 3 and 4, XXXXX still had slight erythema but had disappeared on day 7. Slight oedema was only observed in XXXXX at XXXXX h post application. The evaluator concluded that the product was a slight irritant to XXXXX skin.

Exposure

- The product was not intended for home garden use. As a foliar herbicide, it would be used in XXXXX. Given this frequency of application, the evaluator considered that for any worker using this product, exposure to mesotrione would result from short-term repeat application.
- Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills and equipment. The main route of exposure to the product will be dermal and inhalation, although ocular exposure may also occur.
- The only acute hazard associated with the product was slight skin and eye irritation.

Risk from Repeat Exposure

- There was a potential risk from repeat exposure to this product. However, since the NOEL was derived from repeat-dose study in animals, a margin of exposure (MOE) of 100 or above was considered acceptable for mesotrione in this instance. The MOE took into account both interspecies extrapolation and interspecies variability. MOEs for XXXXX application was acceptable when wearing cotton overalls (or equivalent clothing).

XXXXX.

Re-entry Risk

- The MOEs XXXXX for workers and the public entering treated areas were acceptable on day zero. Therefore, there was no re-entry risk associated with the product after XXXXX.

XXXXX

EXPERT ADVISORY COMMITTEE DISCUSSION

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

Parent entry

Several Members argued that although mesotrione had low acute toxicity, developmental toxicity was potentially an issue, particularly the delayed ossification findings in the absence of maternal toxicity. Some Members argued that the developmental toxicity findings were spontaneous in nature noting that similar effects were observed in the control group. Members generally agreed that these skeletal abnormalities were common developmental effects, and that scheduling would instead be driven by the need to mitigate the irritation potential of mesotrione.

A Member noted that repeated exposures to mesotrione may increase plasma tyrosine metabolism that could lead to ocular effects. The Member noted that the evaluation

report did not provide information on the specific ocular effects and questioned whether the ocular effects could lead to cataracts. Members noted advice from the evaluator that while the report was unclear as to the specifics of the ocular effect, there were clear data from humans who had inhibited tyrosine metabolism that these issues only arose at high tyrosine levels. In light of the limited absorption potential the evaluator suggested, and Members agreed, that this was an unlikely risk.

Several Members asserted that eye irritation was observed only when animals were exposed to higher concentrations (coupled with un-irrigated eyes following exposure) of mesotrione. Some Members also noted that the eye irritancy appeared to be species specific, where it was observed in XXXXX but was not as evident in XXXXX. The Members agreed that eye irritancy risk from mesotrione was sufficiently low as to allow mitigation through a Schedule 5 listing.

Cut-offs

The Committee then discussed whether a low concentration cut-off to exempt from scheduling was likely to be warranted. Some Members argued given its low toxicity and use pattern, that a 50 per cent cut-off may be appropriate. Other Members, however, asserted that there were no data or robust arguments to support that mesotrione at this level was not an irritant. Several Members also noted that two other similar herbicides, namely pyrasulfotole and isoxaflutole, were listed in Schedule 5 with no exemption cut-offs. Members agreed that an exemption cut-off was not appropriate at this time.

Other issues

A Member was also concerned that although the product use indicated that it would be used in XXXXX, Schedule 5 listing of mesotrione may eventually led to diversion to the domestic market. Members noted, however, that other uses for mesotrione would be subject to the APVMA registration process.

Implementation

Members generally agreed that as a new active, there was no need to allow time to run down existing stock or to re-formulate an existing product so a shorter implementation period was sufficient.

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 a shorter implementation period (1 January 2012) was appropriate.

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

DELEGATE'S INTERIM DECISION

The delegate decided to create a new Schedule 5 entry for mesotrione. The delegate decided that an implementation date of 1 January 2012 was appropriate (i.e. three months after publication of the final decision).

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate decided to create a new Schedule 5 entry for mesotrione. The delegate also decided on an implementation date of 1 January 2012.

Schedule 5 – New entry

MESOTRIONE.

1.2 SAFLUFENACIL

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

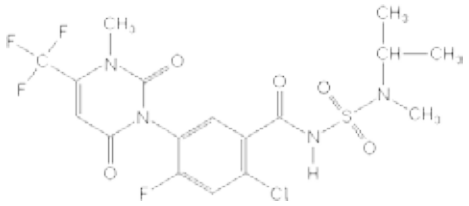
Saflufenacil – proposal to reschedule from Schedule 7 to Schedule 6. The delegate is also seeking advice on potential cut-offs from Schedule 6 to Schedule 5, including the possibility of a 70 per cent cut-off limited to water dispersible granule formulations.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that an exception be created from the Schedule 7 saflufenacil parent entry to Schedule 5 for water dispersible granule preparations. The Committee also recommended an implementation date of no more than 6 months after the delegate's final decision (i.e. 1 January 2012).

BACKGROUND

Saflufenacil is a member of the pyrimidindiones group of herbicides. Saflufenacil is the approved common name (ISO) for N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide which has the structure:



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

In June 2009, the NDPSC decided to include saflufenacil in Schedule 7. The NDPSC particularly noted reports that saflufenacil increased skeletal malformations (bent scapula) at a relatively low dose in the absence of any significant signs of maternal toxicity. The NDPSC was concerned with the bent scapula effect, noting that this was an irreversible effect that was a highly unusual developmental toxicity marker.

In October 2009, the NDPSC considered post-meeting submissions, including new developmental toxicity data, requesting inclusion of saflufenacil in Schedule 6. The new developmental data asserted that there were marked interspecies differences with regard to PPO inhibition by saflufenacil. The NDPSC noted that the study only considered saflufenacil's role in inhibiting one enzyme (PPO), where other PPO inhibitors had not produced the bent scapula effect. It was therefore argued that it was not possible to conclude that only this particular enzyme was responsible for the developmental toxicity effect. The NDPSC decided that the June 2009 Schedule 7 decision remained appropriate until the new data on developmental toxicity had been evaluated through the usual APVMA process.

In February 2010, the NDPSC was advised that XXXXX had updated its 2009 evaluation to include the new developmental toxicity data. The evaluator advised:

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

The February 2010 NDPSC meeting confirmed the June 2009 Schedule 7 decision.

XXXXX subsequently submitted additional data to the APVMA in support of requested changes to the scheduling of XXXXX.

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

SCHEDULING STATUS

Saflufenacil is listed in Schedule 7.

INITIAL SUBMISSIONS

Applicant's Submission

The evaluator recommended:

- Rescheduling saflufenacil from Schedule 7 to Schedule 6, based on developmental toxicity findings in XXXXX but not XXXXX, and *in vitro* data indicating that XXXXX were significantly more sensitive to PPO inhibition than XXXXX together with slight skin and minimal eye irritation.
- An additional cut-off to Schedule 5 for water dispersible granule products containing XXXXX per cent or less saflufenacil, based on slight skin and eye irritation, low dermal absorption of saflufenacil and the large margins of exposure through the use of this formulation.

Other evaluator conclusions included:

- There were no objections on human health grounds to the approval of saflufenacil or XXXXX.
- The ADI for saflufenacil was established at 0.017 mg/kg bw/d based on a NOAEL of 5 mg/kg bw/d (which was also the NOEL) in a developmental XXXXX study and using a 300-fold safety factor.
- The ARfD for saflufenacil was established at 0.017 mg/kg bw/d based on a NOAEL of 5 mg/kg bw/d (which is also the NOEL) in a developmental XXXXX study and using a 300-fold safety factor.
- XXXXX

Members also noted:

- A global joint review toxicology assessment of saflufenacil was conducted by Canada, the US and Australia. Since the XXXXX report relied significantly on this

international work share assessment, XXXXX adopted the NOAEL and LOAEL approach used by the international assessment.

· The database supplied by the applicant was considered to be adequate for the purposes of risk assessment.

Toxicology - TGAC

XXXXX

XXXXX

Data considered at the June 2009 NDPSC meeting

· Saflufenacil exhibits the following toxicological characteristics:

- Saflufenacil had low oral XXXXX, dermal XXXXX and inhalational toxicity XXXXX in XXXXX. It was a minimal eye and slight skin irritant in XXXXX, but not a skin sensitiser in XXXXX.
- Repeat dosing of saflufenacil in XXXXX caused microcytic hypochromic anaemia and porphyria, and clinical chemistry and histopathological changes in the liver, spleen and/or bone marrow.
- Saflufenacil was not genotoxic *in vitro* and *in vivo* tests. There was no carcinogenicity potential found in long-term studies in XXXXX.
- Saflufenacil was not a neurotoxin and reproduction toxin in XXXXX.
- Decreased foetal body weights and increased skeletal malformations and variations, were observed at XXXXX in the absence of maternal toxicity in a XXXXX developmental study. However, developmental toxicity was only seen in XXXXX up to XXXXX, a dose level that produced mortality in dams.

Additional data considered at the February 2010 NDPSC meeting

· Additional data was submitted in the form of an *in vitro* study investigating the relative inhibitory effects of saflufenacil, as well as oxyfluorfen and butafenacil, on PPO activity in liver mitochondrial fractions obtained from XXXXX. The evaluator made the following points in relation to this data:

- The relative inhibitory potency of saflufenacil in XXXXX liver mitochondria was approximately XXXXX-fold higher relative to the XXXXX. Much higher differences in relative inhibition were seen with XXXXX, when compared to the XXXXX.
- The *in vitro* data indicated that XXXXX are significantly more sensitive to PPO inhibition than XXXXX, which was consistent with the *in vivo* developmental findings in XXXXX.

- The *in vitro* study provided no evidence for the MOA of saflufenacil-induced skeletal malformation.
- Saflufenacil showed the lowest overall inhibition of PPO enzyme activity compared to butafenacil and oxyfluorfen, but the relative inhibition across species was consistent across the three chemicals with the greatest potency seen in XXXXX and the least in XXXXX.
- Butafenacil and oxyfluorfen are both more potent PPO inhibitors than saflufenacil *in vitro*, but skeletal effects were only seen with oxyfluorfen, in XXXXX in the absence of maternal toxicity and XXXXX in the presence of marked maternal toxicity.
- The divergent findings in XXXXX developmental studies with butafenacil and oxyfluorfen suggest that inhibition of PPO may not be relevant to the MOA for saflufenacil-induced skeletal malformation.

New Data

· No toxicology studies were submitted with the current application. The applicant provided a dermal absorption study conducted in XXXXX.

Repeat toxicity – further details of previous data

· The primary target of saflufenacil was the haematological system. Consistent with its mode of action as a PPO inhibitor, repeat dosing of saflufenacil in XXXXX caused microcytic hypochromic anaemia, porphyria, changes in clinical chemistry parameters and organ weight change and/or histopathology changes in the liver, spleen and bone marrow. The lowest NOAEL was XXXXX, based on slight anaemia and increased liver porphyrin observed at the next highest dose level.

· The increased porphyrin and bilinogen levels in the plasma, liver and excretions are consistent with the proposed inhibition of PPO.

· However, considering all the available data, it was concluded that increased urobilinogen and porphyrin levels observed at low doses in the absence of other clinical pathology and histopathological changes should generally not be regarded as an adverse effect.

Reproductive and developmental – further details of previous data

· Increased stillborns and XXXXX mortality during the early phase of lactation, together with reduced XXXXX body weight gains were observed at XXXXX in a 3-generation reproduction study in XXXXX. However, saflufenacil did not affect reproductive performance or the reproductive system.

· In a XXXXX developmental study, decreased foetal body weight and increased skeletal malformations (bent scapulae, thick humeri, bent radii, ulnas and femurs, malpositioned and bipartite sternebrae, and wavy ribs) and variations (incomplete ossification in the nasal area) were observed at XXXXX in the absence of maternal

toxicity. In contrast, increased abortion was seen in a XXXXX developmental study but only at a dose level that caused severe maternal toxicity (e.g. mortality in dams).

- With regard to the XXXXX being significantly more sensitive to the developmental toxicity potential of saflufenacil compared to XXXXX, an *in vitro* assay investigating the inhibition of PPO activity in the liver demonstrated significant inter-species differences in saflufenacil inhibition of PPO. The data indicated that saflufenacil inhibition of PPO was comparable in XXXXX, and was significantly less than that seen in XXXXX. However, the MOA for saflufenacil-induced skeletal malformation had not been established.
- The lowest NOAEL (and also the NOEL) for developmental toxicity, was XXXXX in the XXXXX developmental study.
- Given the occurrence of foetal toxicity in a developmental toxicity study, including skeletal malformations in the absence of maternal toxicity, an extra safety factor was considered necessary to protect women of child bearing age. The choice of an appropriate extra safety factor value was undertaken using expert judgement and consideration of the following observations:
  - Compared to concurrent controls, there was a statistically significant decrease in mean foetal body weight (both sexes combined) of XXXXX in the mid XXXXX and high dose XXXXX groups.
  - A statistically significant increase in incomplete ossification of the nasus in the mid XXXXX and high dose XXXXX groups.
  - A XXXXX incidence of bent scapula at the mid dose and XXXXX incidences at the high dose XXXXX.
- Bent scapula and incomplete ossification of the nasus had not been observed in a historical database of XXXXX foetuses. However, it was noted and accepted that while the observed decrease in body weight gain was treatment related (i.e. followed a dose response relationship) the decrease of XXXXX per cent at the mid dose was close to the average statistical weight of the testing facility and, thus, may simply reflect biological variation.
- Overall, the treatment related findings at the mid dose of XXXXX were limited and minimal with regards to their incidence and toxicological nature. This suggested that XXXXX was likely to be close to the NOAEL/LOAEL threshold for developmental toxicity. Furthermore, the NOAEL (and NOEL) of XXXXX for developmental toxicity was XXXXX -fold lower than the identified maternal NOAEL of XXXXX, at which the observed maternal effects (increased porphyrin and urobilinogen in the plasma) were not considered adverse (but were indicators of exposure).
- Hence, in consideration of the above, an extra 3-fold safety factor was considered appropriate for derivation of relevant health standard values.

Hazard Classification

- Saflufenacil is listed in Safe Work Australia's Hazardous Substances Information System Database, with the risk phrase: Xn (Repr. Cat. 3; R63) '*Possible risk of harm to the unborn child*' for preparations containing 5 per cent or more of saflufenacil.
- The evaluator has also provided the Globally Harmonised System of classifications (GHS) based classification for saflufenacil according to the GHS (OECD, 2009):

NOHSC Classification	GHS Classification	Hazard Communication
Xn; Repr. Cat 3 R63 Possible risk of harm to the unborn child	Reproductive toxicity Category 2	Warning  Suspected human reproductive toxicant (developmental effects)

Scheduling of TGAC – evaluator's conclusions

- Saflufenacil acts as a PPO inhibitor, and the evaluator proposed that on the basis that saflufenacil was not a developmental toxicant in XXXXX and *in vitro* data indicated that XXXXX were significantly more sensitive to PPO inhibition than XXXXX, Schedule 6 was more appropriate than Schedule 7.
- Additionally, while the evaluator noted the concern expressed by the NDPSC in February 2010 that there was uncertainty in the MOA for developmental effects in one laboratory species XXXXX, the evaluator argued that this was often the case for new active constituents that had a developmental toxicity potential. The only other hazards observed for saflufenacil were slight skin and minimal eye irritation in XXXXX.

Toxicology - Product (water dispersible granule)

- The product was a wettable granule formulation containing XXXXX saflufenacil. No toxicology data were provided on the product with this application.
- The toxicity of the product was evaluated in the 2009 XXXXX report. It was of low acute oral, dermal and inhalational toxicity in XXXXX. It was a slight skin and eye irritant in XXXXX, but was not a skin sensitiser in XXXXX.

XXXXX

Product exposure and risk assessment

XXXXX

Exposure

- The product was not intended for domestic use.
- Since saflufenacil was a herbicide designed for XXXXX the exposure potential for farmers and their workers would generally be expected to be limited to short-term periods.
- The main routes of exposure would be dermal and inhalation. Workers may be exposed to the product when opening containers, mixing/loading, application, and cleaning up spills, maintaining equipment and entering treated areas.
- It was unlikely that application of the product would pose any significant exposure risks to bystanders during application or re-entry to the treated areas, including re-entry to treated public service areas.

Risk assessment – NOAEL selection

- There was no repeat dose inhalational study available.
- The lowest NOAEL (and NOEL) in a short term study was XXXXX from a XXXXX developmental study based on decreased foetal body weights and increased skeletal malformations and variations at XXXXX without maternal toxicity.
- The evaluator considered that it was appropriate to use the NOAEL from this oral developmental study in the XXXXX, together with the warning statement '*Do not use if pregnant'* to dissuade pregnant women from using saflufenacil-containing products.
- Noting the recommendation for the warning statement, the evaluator considered that it was still appropriate to take a precautionary approach and apply an extra safety factor of 3 to account for potential developmental concerns in addition to inter- and intra-species variability. Thus, a NOAEL of XXXXX derived from the XXXXX developmental study was selected for the occupational risk assessment of saflufenacil during mixing/loading, application, and re-entry, and a MOE of 300 [taking into account inter-species variability (10), intra-species (10) variability and the developmental concerns (3)] was considered appropriate.

Risk assessment

- In the 2009 and 2010 evaluations, a dermal absorption factor of 100 per cent was used in the OHS risk assessment for the product. This was based on a submitted dermal absorption study conducted using an emulsifiable concentrate formulation (EC) which showed a high rate of dermal penetration (XXXXX per cent). However, it was now considered that this high dermal penetration rate of saflufenacil was the result of skin damage caused by the organic solvent in the EC formulation.
- In the current evaluation, a dermal absorption study conducted in rats with a suspension concentrate (SC) formulation containing XXXXX saflufenacil was

considered. It was concluded that dermal absorption values obtained from the SC formulation would be the most suitable for use in the risk assessment for the water dispersible granule product XXXXX and the evaluator expected that the rate of dermal absorption of saflufenacil from a liquid-based SC formulation would be higher than a granule-based formulation at high concentrations. It was found that saflufenacil in the SC formulation had a very low dermal absorption rate in XXXXX. Thus, a dermal absorption factor of XXXXX per cent was used in the risk assessment.

- The occupational risk assessment (using a dermal absorption factor of XXXXX per cent) indicated that absorption of saflufenacil in workers without gloves and wearing a single layer of clothing using the product in accordance with proposed use patterns was low and unlikely to reach systemic exposure levels that would cause a concern for potential developmental effects.
- A 70 kg worker would need to be orally exposed to approximately XXXXX saflufenacil daily to reach the XXXXX LOAEL of XXXXX for developmental effects. However, the highest systemic exposure in workers was estimated to be XXXXX during mixing and application of saflufenacil for hand application with low pressure hand wand. Thus, a very high margin of safety existed between worker exposure levels and the dose level at which developmental effects were observed in XXXXX, and was indicated by MOEs > 4200 for all the proposed application methods.
- The low systemic exposure estimated in the risk assessment was because of the low application rates proposed for various scenarios together with the low dermal absorption of saflufenacil as indicated by the newly submitted data.
- The evaluator noted the influence the formulation could have on the dermal absorption of saflufenacil, with approximately XXXXX per cent absorbed for an EC formulation (through the integrity of the skin being compromised due to the corrosive/irritant properties of the formulation).

<u>Hazard Classification</u>

- The evaluator concluded that the product should be classified the same as the TGAC saflufenacil, i.e. a hazardous substance according to the NOHSC criteria, with the same risk phrases. The GHS based classification was also provided by the evaluator, and was also the same as for saflufenacil.

<u>Product – Evaluator's conclusion</u>

- Based on the low dermal absorption of saflufenacil and substantial MOEs calculated for all the stipulated application methods of the product, together with slight skin and eye irritation in XXXXX, a cut-off to Schedule 5 for water dispersible granule products containing XXXXX per cent or less saflufenacil was proposed.

Applicant's Response to the Evaluation Report

The evaluator advised that the applicant had accepted the findings and recommendations of the XXXXX report.

June 2011 Pre-meeting Submissions

A single pre-meeting submission was received from XXXXX supporting the proposed rescheduling. This submission advised:

- XXXXX.
- Following the global joint review toxicology assessment of saflufenacil a product was subsequently launched in the US and Canada.

The submission also provided some information specifically addressing section 52E matters as follows:

Dosage and formulation

- XXXXX noted that the original XXXXX application to the APVMA considered two alternative formulations: XXXXX.
- For clarity, since the original submission to APVMA was many years ago, only one product was now intended to be commercialised, namely the XXXXX.

Labelling, packaging and presentation of a substance

- Reiterated that the XXXXX product would bear the brand name XXXXX. The proposed pack size for launch was XXXXX.

February 2010 NDPSC Consideration

ACCS Members noted the following from the February 2010 NDPSC discussion:

- While it was highly concerning that saflufenacil had been observed to cause severe malformations in the foetus (bent scapula) without concomitant maternal toxicity, several NDPSC Members noted that this had only been observed in one species and questioned the significance of this effect and its relevance to humans. Another NDPSC Member asserted that, had the bent scapula effect been observed in more than one species, it would likely have been considered a human reproductive toxicant, but with results in only one species, this was not a high intensity signal of concern.
- An NDPSC Member asserted that if the human reproductive concern was not particularly relevant to humans (and in any case may be reduced by labelling from the registration process), then the toxicological profile of saflufenacil (low acute oral, dermal and inhalational toxicity) suggested a Schedule 6 classification. Particular reference was made by the Member to the need for access, noting effectiveness against resistant weeds and potential to replace various highly toxic herbicides such as paraquat or atrazine. Another Member asserted, however, that although bent scapula was exhibited in only one species, the effect was dose related and occurred at

two doses in the absence of maternal toxicity, and therefore should be considered as a significant concern for human reproductive toxicity.

- Several NDPSC Members also remained concerned that there was uncertainty regarding the MOA for the bent scapula effect, noting that it was always difficult to extrapolate effects in a single species to human risk. In particular, the applicant's argument that this effect would not be a risk for humans relied on data that demonstrated that there were marked interspecies differences with regard to PPO inhibition by saflufenacil. However, this relied on an assumed central role of PPO inhibition in causing the bent scapula effect. Several Members remained unconvinced that this association had been adequately established.
- The NDPSC generally agreed that, while only observed in one species and therefore not a clear human developmental hazard, on balance the uncertainty on the MOA giving rise to the bent scapula effect supported a careful approach until such time as more robust arguments could be presented to reassure the NDPSC that this was not a significant risk to human health.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally 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 (d) the formulation, packaging and presentation.

Parent entry

The Committee debated whether the fact that the developmental toxicity had been observed in only one species was sufficient reassurance that it was unlikely to be relevant to humans. Members agreed that this was the key question in determining whether the saflufenacil parent entry could be rescheduled from Schedule 7 to Schedule 6.

A Member asserted that Schedule 7 was too severe for a single species effect. Another Member noted that saflufenacil products had been registered overseas with conditions less restrictive than Schedule 7. However, several Members argued that just because the effects had only been observed in one species did not necessarily mean that this would not be relevant to humans, noting that this had been the case for thalidomide.

A Member observed that the previous NDPSC concerns about the uncertainty of the MOA for the developmental toxicity (bent scapula, a rare effect observed at exposures significantly lower than maternal toxicity), remained unaddressed. The Member maintained that it was not possible to establish the relevance of the developmental toxicity findings to humans.

A Member noted that the evaluator's recommendations regarding the down scheduling of saflufenacil were largely based on new absorption data (i.e. systemic uptake of saflufenacil was very low, significantly reducing the risk from saflufenacil exposure). The Member argued, and the Committee generally agreed, that while this may be grounds

for reducing scheduling controls on the formulation exhibiting this low absorption (water dispersible granule preparations), it was not appropriate to extrapolate this to all formulations, particularly as questions remained regarding the MOA for the observed developmental toxicity effects.

The Committee generally agreed with the February 2010 NDPSC conclusion that, while the developmental toxicity effects were only observed in one species and therefore did not translate to a clear human developmental hazard, on balance the uncertainty on the MOA giving rise to the bent scapula effect supported a conservative approach until such time as more robust arguments could be presented to show that this was not a significant risk to human health.

Cut-off

A Member noted that the evaluator had asked for a cut-off for water dispersible granule products containing XXXXX per cent or less saflufenacil. Several Members suggested that the percentage component was unnecessary, particularly as the toxicity difference between the high concentration cut-off and the 100 per cent substance was likely to be minimal. The risk mitigation in this case was arising from the very low dermal absorption potential from the water dispersible granule presentation.

A Member noted that there was potential for use of this formulation in public areas and queried whether this was a concern. In particular, the Member queried whether the low dermal absorption for the water dispersible granules extended to the subsequent sprayed application. Another Member asserted that the evaluator had satisfactorily addressed this specific issue – the MOE's were very high so there was no basis for concern relating to bystander exposure.

Members then discussed whether, in considering a cut-off, this should be to Schedule 5 or Schedule 6. A Member argued that a move from Schedule 7 to Schedule 5 was substantial and could convey an inappropriate message in relation to the risks of the parent compound. Other Members asserted, and the Committee generally agreed, that the substantial MOEs calculated for all the stipulated application methods of this formulation, together with only slight skin and eye irritation concerns, would allow a Schedule 5 classification, so long as this was restricted to water dispersible granule preparations.

Implementation

A Member asserted, and the Committee generally agreed, that there was no reason to delay the implementation of the saflufenacil scheduling changes.

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 to an early implementation period i.e. 1 January 2012.

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

DELEGATE'S INTERIM DECISION

The delegate decided to create an exception from the Schedule 7 saflufenacil parent entry to Schedule 5 for water dispersible granule preparations. The delegate also decided an implementation date of 1 January 2012.

SUBMISSIONS ON INTERIM DECISION

A submission on the delegate's interim decision on saflufenacil was received from XXXXX. The submission supported the delegate's interim decision to create an exception from Schedule 7 saflufenacil parent entry to Schedule 5 for water dispersible granule preparations.

DELEGATE'S FINAL DECISION

The delegate decided to create an exception from the Schedule 7 saflufenacil parent entry to Schedule 5 for water dispersible granule preparations. The delegate also decided on an implementation date of 1 January 2012.

Schedule 5 – New entry

SAFLUFENACIL in water dispersible granule preparations.

Schedule 7 – Amendment

SAFLUFENACIL – Amend entry to read:

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

1.3 PYROXASULFONE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

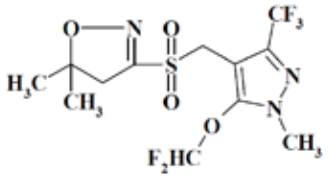
Pyroxasulfone – proposal to include in Schedule 7. The delegate is also seeking advice on potential cut-offs from Schedule 7 to Schedule 6, including the possibility of an 85 per cent cut-off limited to pre-emergence herbicide use.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 7 entry be created for pyroxasulfone with a cut-off to Schedule 6 for water dispersible granule preparations when used as a pre-emergence herbicide. The Committee also recommended an implementation date of no more than 6 months after the delegate's final decision (i.e. 1 January 2012).

BACKGROUND

Pyroxasulfone is the approved common name for a pre-emergence herbicide discovered amongst a series of herbicidal 3-sulfonylisoxazoline derivatives. Pyroxasulfone has been shown to inhibit the biosynthesis of very long chain fatty acids in plants, causing a build up of fatty acid precursors. The structure of pyroxasulfone is:



XXXXX sought XXXXX approval of a new active ingredient pyroxasulfone and XXXXX. Pyroxasulfone has activity against both grass and broadleaf weeds and selectivity on broad acreage crops. No other potential use pattern, apart from use as a herbicide, was identified.

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

SCHEDULING STATUS

Pyroxasulfone is not currently specifically scheduled, nor does there appear to be any entries which would capture pyroxasulfone either as a derivative or through a group entry.

INITIAL SUBMISSIONS

Applicant's Submission

Based on the toxicity profile, the evaluator recommended that pyroxasulfone be included in Schedule 7. A cut-off to Schedule 6 was proposed for pre-emergence herbicides containing XXXXX or less of pyroxasulfone based on the short-term use pattern, appropriate short term dermal and inhalational studies available for the risk assessment and margins of exposure approximately twice that required through use of this formulation.

Other evaluator conclusions included:

- There were no objections on human health grounds to the approval of pyroxasulfone XXXXX.
- The ADI for pyroxasulfone was established at 0.002 mg/kg bw/d based on a NOAEL of 2.05 mg/kg bw/d in a XXXXX -yr dietary study in XXXXX, which is supported by the NOEL in a XXXXX -yr oral study in XXXXX, using a refined 1000-fold safety factor consisting of safety factors of 10 for potential intraspecies and interspecies variation, and an additional safety factor of 10 to account for the seriousness of the health effect of concern.
- The ARfD for pyroxasulfone was established at 0.1 mg/kg bw/d based on a NOAEL of 100 mg/kg bw/d in a developmental neurotoxicity study in XXXXX, using a refined 1000-fold safety factor consisting of safety factors of 10 for potential intraspecies and interspecies variation, and an additional safety factor of 10 to account for the seriousness of the health effect of concern.
- XXXXX

Toxicology

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

XXXXX

- Following oral administration in XXXXX, pyroxasulfone was rapidly well absorbed, broadly distributed and fully excreted largely via the urine and faeces.
- Pyroxasulfone was of low acute oral, dermal and inhalational toxicity in XXXXX. It was a slight irritant to eyes and non-irritant to the skin of XXXXX. It was not a skin sensitiser in XXXXX.
- While pyroxasulfone was not toxic following acute dermal exposure in XXXXX, it was moderately toxic in XXXXX following a XXXXX -week dermal exposure producing local inflammation and systemic effects of minimal to mild cardiac

myofiber degeneration. Pyroxasulfone was not toxic by the inhalation route in a XXXXX -d study.

- The primary target of toxicity following repeated administration of pyroxasulfone in XXXXX appeared mainly to be the muscular and the nervous systems with effects seen at low doses in repeat dose oral studies in XXXXX, while muscular toxicity was seen at high doses in a XXXXX repeat dose dermal study.
- Both XXXXX appeared equally sensitive to the effects of pyroxasulfone XXXXX. While the toxic endpoints in XXXXX were muscular and sciatic nerve degeneration, the effects in XXXXX included bladder mucosa hyperplasia and bladder transition cells papilloma in addition to cardiomyopathy and sciatic nerve effects. Other effects produced by pyroxasulfone included cardiac toxicity (increased cardiomyopathy in XXXXX), liver toxicity (centrilobular hepatocellular hypertrophy) and kidney toxicity (increased incidence of chronic progressive nephropathy in XXXXX).

Carcinogenicity

- In a carcinogenicity study in XXXXX, renal tubular adenomas were observed in XXXXX at a dietary dose of XXXXX. However, a pathology re-analysis of the kidney slides indicated that the 'renal tubular hyperplasia' originally observed were more accurately defined as dilated proximal tubules with simple hyperplastic lining (i.e. simple tubular hyperplasia) which was not generally considered a precursor to renal tubule neoplasia. Additionally, the lack of cell necrosis and regeneration, which were known to lead to precursor lesions such as atypical tubular hyperplasia, suggested that the observed simple tubular hyperplasia was unlikely to be a precursor to a carcinogenic event in this case. Furthermore, the reported incidence of renal tubular adenoma in XXXXX did not reach statistical significance when compared with concurrent control data and were only slightly outside the maximum historical range XXXXX. Thus, pyroxasulfone was not considered to be carcinogenic in XXXXX.
- In XXXXX, urinary bladder transitional cell papillomas and a single bladder carcinoma were observed in males only at or above XXXXX. A pathology re-analysis of the bladder slides used as the basis for the histopathological reporting was undertaken to detect evidence of cytotoxicity and necrosis. The finding reported as a carcinoma was re-diagnosed as a diverticulum of the bladder instead of a malignant tumour.
- The applicant postulated that the mode of action for carcinogenicity in XXXXX involves a non-genotoxic response leading to increased cell proliferation resulting from site-specific cytotoxicity/irritation, followed by compensatory regenerative cell proliferation, leading to hyperplasia and subsequent benign lesions (in this case, papillomas in urinary bladder). The evaluator noted, however, that the carcinogenic effects only occurred at very high threshold doses relative to expected human exposures. This non-genotoxic mode of action possibly involved urinary microcrystals.

- While clear cellular hyperplasia was observed, the lack of primary evidence in pyroxasulfone studies linking the presence of urinary solids to urothelial irritation, and the uncertain identity of the urinary solids (which were seen infrequently, including in control animals) remain data gaps; hence, in proposed mode of action. The limited strength of evidence for cellular necrosis also diminishes the weight of evidence for the proposed mode of action, though this is countered somewhat by the increased labelling bromodeoxyuridine (BrdU) index values observed with pyroxasulfone treatment at XXXXX. BrdU is a synthetic thymidine analogue that gets incorporated into DNA when a cell is dividing; hence can be used to detect proliferating cells.
- The evaluator concluded that, from a toxicological hazard perspective, it was considered that there was insufficient evidence proving that the observed urinary bladder transitional cell papillomas in XXXXX at doses of XXXXX would not be relevant to humans. Thus the mode of action for the observed tumours has not been established and it has not been demonstrated that the observed bladder tumours in XXXXX would not be applicable to humans.

Mutagenic/Genotoxic potential

- Pyroxasulfone was not considered to be genotoxic *in vivo*, and was not a reproductive toxicant in XXXXX or teratogenic in XXXXX. Furthermore, pyroxasulfone did not produce immunotoxic effects in XXXXX.

Reproductive toxicity

- There was no evidence of a reproductive toxicity potential in XXXXX studies, including doses that produced pronounced parental toxicity. Pyroxasulfone did not exhibit teratogenicity in the XXXXX at the limit dose of XXXXX and though it exhibited slight developmental toxicity in XXXXX (reduced fetal weight and resorptions) at XXXXX; the severity of these effects at the limit dose were not considered sufficient for pyroxasulfone to be considered a hazard for teratogenicity. However, effects were seen in a XXXXX (delayed) developmental neurotoxicity study as discussed below.

Neurotoxicity

- Although pyroxasulfone produced neurotoxic effects in XXXXX (impaired hind limb function, ataxia, tremors, and axonal/myelin degeneration of the sciatic nerve), XXXXX (sciatic nerve lesions), specific neurotoxicity tests did not reveal neurotoxic effects.
- However, in a developmental neurotoxicity study in XXXXX, at XXXXX a dose related decrease in absolute brain weight accompanied with a decrease in the thickness of the hippocampus, corpus callosum and cerebellum was seen in female offspring on postnatal day XXXXX, with a decrease in absolute brain weight seen in males at XXXXX. These findings were seen in the absence of maternal toxicity. Dosing was ceased at day XXXXX, however, on postnatal day XXXXX a decrease was still observed in absolute brain weight in male and female offspring from the

XXXXX dose group, along with a decrease in the thickness of the hippocampus in females. Although no clear effect of treatment was seen on Functional Observation Battery (FOB) performance it was noted that neurotoxic effects have been observed in XXXXX in chronic studies.

· Therefore, the available evidence indicated that the nervous system was a target organ for pyroxasulfone activity. Consequently, the findings of decreased absolute brain weight and morphological changes present a neurological concern for the developing foetus, baby and child which would likely be more susceptible to the developmental neurotoxicity potential of pyroxasulfone. These data indicated pyroxasulfone was a developmental toxicant.

Hazard classification

· Pyroxasulfone was not listed on the Safe Work Australia's Hazardous Substances Information System (HSIS) Database. The evaluator has determined that pyroxasulfone should be classified as a hazardous substance according to NOHSC Approved Criteria for Classifying Hazardous Substances, with the following risk phrases:

- T: R61 (Repr. Cat. 2) May cause harm to the unborn child.
- Xn; R40 (Carc. Cat. 3) Limited evidence of a carcinogenic effect.
- Xn; R48/22 Danger of serious damage to health by prolonged exposure if swallowed.

To be applied at the following concentrations:

- ≥ 10 % T; R61, R40, R48/22
- 10 % < Conc. ≤ 1 % T; R61, R40
- 1 % < Conc. ≤ 0.5 % T; R61

· Classification in Category 2 as a developmental toxicant was considered appropriate as, while the developmental neurotoxicity effects described above were seen in the only species tested for delayed neurotoxicity, effects on the nervous system have been observed in repeat dose oral studies in XXXXX. The systemic toxicity data support the view that the nervous system was a target organ for pyroxasulfone toxicity. Consequently, there were strong concerns that the developing foetus, baby and child would be susceptible to the (delayed) neurotoxicity potential of pyroxasulfone and thus Category 2 instead of Category 3 was considered more appropriate in this instance.

· Classification as a Category 3 carcinogen was considered appropriate as benign bladder tumours (bladder transitional cell papillomas) were seen in XXXXX at a dose level of XXXXX, while no treatment related tumours were seen in female XXXXX. Additionally, it should be noted that pyroxasulfone did not produce treatment related tumours in XXXXX and was not mutagenic or genotoxic *in vitro*, and was not considered to be genotoxic *in vivo*.

- Classification for harmful repeat dose effects by the oral route (R48/22) was justified as myocardial degeneration was observed at approximately XXXXX in a XXXXX d oral study in XXXXX, and muscular as well as axonal/myelin degeneration in the sciatic nerve and spinal cord was seen at XXXXX in a XXXXX -d oral study in the XXXXX.

Scheduling comments

- The evaluator considered that the developmental neurotoxicity potential met the criteria for Schedule 7, while the observed benign tumours seen in one species in one sex met the Schedule 6 criteria, as did the observed toxicity to the muscular and nervous system at the observed oral doses.
- Consequently, pyroxasulfone was a developmental toxicant and was considered to be highly toxic to pregnant women and children, thus the recommendation that a listing in Schedule 7 was appropriate.

Members also noted that the product (XXXXX per cent pyroxasulfone) shared the same acute toxicity profile as pyroxasulfone, with the exception that it was a skin sensitiser.

XXXXX

Exposure

- The product was a XXXXX formulation not intended for home garden use. It was expected it will be applied once per season, and will be diluted prior to use. It was unclear from the label whether the farmer or contractors were likely to carry out this activity.
- Given this frequency of application, the evaluator considered that for any worker using this product, exposure to pyroxasulfone would result from short-term repeat application.
- The potential routes of exposure to the product were dermal, inhalation and possibly ocular. The most likely route of exposure was dermal. As worker exposure to pyroxasulfone would result from short-term repeat application, the most appropriate studies from which to choose a NOEL for OH&S risk assessment would be a short term repeat dermal study.
- No dermal absorption studies were submitted for evaluation. However, pyroxasulfone was toxic to XXXXX following a XXXXX -week dermal exposure producing local inflammation and systemic effects of minimal to mild cardiac myofiber degeneration at the limit dose of XXXXX. A NOAEL of XXXXX was identified for this systemic health effect in this study. This study indicated that pyroxasulfone could be absorbed across the skin, and as an appropriate dermal study was available for the OHS risk assessment, adjustment of the NOAEL for dermal absorption was unnecessary.
- Additionally for the OHS risk assessment, a XXXXX -week inhalation study was available in the XXXXX. In this study, no treatment related effects were seen up to

and including the highest concentration tested. Thus, the NOAEC for this study was XXXXX.

- Noting the concerns for systemic toxicity, carcinogenicity and developmental neurotoxicity, a maximum additional safety factor of 10, in addition to the default 100 fold safety factor for potential inter- and intra-species, was applied for the OHS risk assessment of the product.
- This MOE was approximately twice the MOE of 1000 which was considered to be acceptable with the inclusion of an additional safety factor to account for the seriousness of the health effect seen in experimental animals following repeated exposure.

Scheduling comments

- The risk assessment was conducted with appropriate XXXXX studies being available for the potential routes of exposure and provided an MOE of approximately XXXXX for a worker wearing a single layer of cotton overall whether gloves were worn or not.
- It was noted that the product had a short term use pattern, and to further mitigate the risk for the potential health effects of concern the proposed label included '*WARNING: Children and pregnant women should not come into contact with this product*' and '*Limited evidence of a carcinogenic effect*' to further ensure that public health objectives were met.
- Consequently, for the proposed use pattern and application a cut-off to Schedule 6 was recommended – but solely for pre-emergence herbicides containing XXXXX per cent pyroxasulfone. It was noted that the acute health effect of skin sensitisation met the criteria for Schedule 6. Members noted, however, that this end-point appeared to be the result of the formulation (excipients/solvents) rather than due to the pyroxasulfone component.

XXXXX

- XXXXX

Applicant's Response to the Evaluation Report

XXXXX had seen the evaluator's report and agreed with the proposed scheduling, noting an intention to make a substantial pre-meeting submission should the matter be referred to the ACCS. Members noted that no such submission was subsequently received.

June 2011 Pre-meeting Submissions

No submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally 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 (d) the formulation, packaging and presentation.

A Member suggested, regarding the observed incidence of bladder lesions in XXXXX but not in XXXXX, that the metabolites present in the urine of each of these groups could have been different and that there may have been an irritant in the urine of XXXXX which was not present in the urine of XXXXX. The Member suggested that such a substance may well have been produced by P_{450} type metabolism in the kidney. The Member was disinclined, therefore, to regard the kidney papillomas seen in XXXXX as examples of neoplasia but rather the results of chronic irritation with prolonged repeat dosing.

A Member noted that while there were minimal acute toxicity issues, there were serious repeat dose concerns, noting effects on the cardiac muscle even in short term studies. In longer term studies, in addition to the cardiac concerns, there were nerve tissue effects at quite low exposure levels, and developmental neurotoxicity was observed. The Member noted that high MOEs had been determined by the evaluator. However, the Member felt that the severity of the endpoints was such that the Committee could not ignore the possibility of exposure. The Member argued, and the Committee generally agreed, that Schedule 7 was appropriate for the pyroxasulfone parent entry.

Cut-off

A Member noted that the evaluator had asked for a cut-off to Schedule 6 for products containing XXXXX per cent or less pyroxasulfone when for pre-emergence herbicidal use. Several Members suggested that the percentage component was unnecessary, particularly as the toxicity difference between the high concentration cut-off and the 100 per cent substance was likely to be minimal.

A Member noted that the likely exposure to pyroxasulfone given the use pattern was dermal and via inhalation, and that repeat dermal exposure was the main concern. A Member argued that this concern was significant enough to not allow any cut-offs from a Schedule 7 parent entry. Several other Members contended, however, that this concern was sufficiently mitigated for water dispersible granule formulations, due to their lower absorption potential. The Members suggested that this presentation could be the basis for a cut-off to Schedule 6. The Committee agreed, noting the high MOEs determined by the evaluator for the water dispersible formulations, its minimised exposure potential and the additional risk mitigation measures intended to be implemented by the regulator through labelling.

The Committee noted concerns that the high MOEs for the water dispersible formulations had presumed short term exposure. Members noted that although the evaluator had considered a worst case scenario of multiple use on a number of farms in a season by a

contractor, this still presumed an overall short term exposure scenario as the intended use was restricted to once per season. Members agreed that this was reasonable for pre-emergence herbicidal use, but were concerned if alternative use-patterns emerged that saw longer term repeated use, particularly given that some of the longer term effects were seen at low exposure levels. Members agreed to additionally restrict the cut-off to Schedule 6 to those products for pre-emergence herbicidal use to mitigate risks of leakage for long-term use.

Implementation

A Member asserted, and the Committee generally agreed, that there was no reason to delay the implementation of the pyroxasulfone scheduling.

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 to an early implementation period of 1 January 2012.

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

DELEGATE'S INTERIM DECISION

The delegate decided to create a new Schedule 7 entry for pyroxasulfone with a cut-off to Schedule 6 for water dispersible granule preparations when used as a pre-emergence herbicide. The delegate also decided on an implementation date of 1 January 2012.

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate decided to create a new Schedule 7 entry for pyroxasulfone with a cut-off to Schedule 6 for water dispersible granule preparations when used as a pre-emergence herbicide. The delegate also decided on an implementation date of 1 January 2012.

Schedule 6 – New entry

PYROXASULFONE in water dispersible granule preparations when for pre-emergence herbicide use.

Schedule 7 – New entry

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

1.4 NAPHTHALENE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Naphthalene – proposal to increase the current restrictions through scheduling on domestic use of naphthalene, including (but not necessarily limited to) mothballs, blocks, discs, pellets or flakes. The delegate is particularly seeking advice on:

- Expanding the container requirements for domestic use of camphor and naphthalene under SUSMP Part 2, Labels and Containers, paragraphs 28 and 29 to apply to flake forms of naphthalene.
- Rescheduling some, or all, forms of naphthalene for domestic use from Schedule 6 to Schedule 7 or Appendix C. This consideration may include the potential for a low concentration cut-off.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

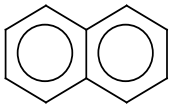
The Committee recommended that the term "flake" be included in SUSMP Part 2 Labels and Containers paragraphs 17, 28 and 29. In addition to this, the Committee recommended that the term "flake" be included in the Appendix F, Part 3 entries for camphor and naphthalene. The Committee also recommended that the existing Schedule 6 naphthalene entry be amended to exclude liquid hydrocarbons when present as impurities.

The Committee recommended an implementation period of at least six months after the delegate's final decision (earliest 1 May 2012).

BACKGROUND

Naphthalene, a white crystalline powder with a characteristic odour, is used as a starting material for a variety of industrial chemicals, dyes, resins, solvents, lubricants and fuel components. Naphthalene is also a moth repellent and insecticide.

The IUPAC name for naphthalene is bicyclo[4.4.0]deca-1,3,5,7,9-pentene and the structure is:



Naphthalene is most commonly encountered by the public as mothballs or toilet deodorant blocks, but the compound is also generated from burning wood or tobacco and as a component of the essential oils of some medicinal and culinary herbs. An estimate of the background exposure to naphthalene from plant sources was not possible from the limited data available but was likely to be quite small given the limited number of plants reported to contain it.

When used as a pest control product, naphthalene is an insecticide in the form of mothballs or flakes for control of moth and larvae which are destructive to textiles made of natural fibres. The products are placed in wardrobes, drawers, bedding stores, and similar areas where the naphthalene vapours can build up to levels toxic to the adult or larvae forms of the moth.

Insecticide use of naphthalene is regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA), and products must comply with the APVMA's requirements, including labelling.

Cases of naphthalene poisoning in members of the public are regularly reported. The taste of naphthalene is not offensive to all people as children have been known to eat mothballs and toilet deodorant blocks, and case reports are available of pregnant women sucking on mothballs.

The APVMA, prompted by a 2011 publication in the Medical Journal of Australia (MJA), sought advice from XXXXX on the adequacy of current safety warnings when used as an insecticidal fumigant in mothballs and related products and the public health risks from exposure by routes other than ingestion, including inhalation.

The 2011 MJA publication (accessible at www.mja.com.au/public/issues/194_03_070211/letters_070211_fm-1.html) described three cases of kernicterus (bilirubin accumulation in the brain) in babies with glucose-6-phosphate dehydrogenase (G6PD) deficiency in Australia in the past three years, one of which was associated with exposure to naphthalene in mothballs. One of the three babies with kernicterus died but it was not stated whether the deceased child was the baby exposed to naphthalene. The publication also reported that the NSW Poisons Information Centre (PIC) had received about one call per week concerning children exposed to naphthalene over the last six years but no accompanying information on exposure circumstances, symptomology, adverse outcomes or verification was provided.

The XXXXX report included scheduling recommendations for naphthalene. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was required.

SCHEDULING STATUS

Naphthalene (except its derivatives) is listed in Schedule 6. Camphor and various naphthalene forms (block, ball, disc or pellet form) except flake forms, are listed in Part 2 (Labels and Containers) 17, 28 and 29. Further naphthalene is listed in Appendix E, Part 2 (First Aid Instructions), Appendix F, Part 3 (Warning Statements and General Safety Directions) and Appendix G (Dilute Preparations).

INITIAL SUBMISSIONS

XXXXX **Report**

The evaluator recommended that:

- APVMA should give consideration to discontinuing registration of naphthalene products in loose flake form, since oral, dermal and inhalational exposure are all more likely with this form.
    - Members noted that on 7 June 2011, the APVMA issued a media release indicating that based on the Department of Health and Ageing advice, as of 6 July 2011 it took action to stop the supply of naphthalene loose flake products for domestic use. The release further indicated the reason for the withdrawal was that packaging and warning statements on these products may not be adequate to protect G6PD deficient individuals and young children exposed to treated fabrics from inhalation and ingestion risks. The APVMA also advised that naphthalene block and ball products were not impacted by this decision.
- Relevant warning statements were required by regulation, but the actual product labels of existing naphthalene products did not generally reflect these requirements. It was possible that this lack of proper labelling had contributed to the recent reports of serious cases of poisoning. The evaluator recommended that the APVMA consider possible action to ensure compliance.
- The current "*Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals"* (FAISD) entries for naphthalene products required review. XXXXX. The FAISD safety directions for naphthalene were appropriate for domestic products that were supplied in tamper proof containers. To reduce the risk to human health from domestic use of naphthalene products, all such products should be required to be presented in tamper-proof containers.
- A first step to risk mitigation would be to include the term 'flake' in SUSMP Part 2 Labels and Containers paragraphs 28 and 29. If the Committee agreed to this, it was recommended that it may also wish to consider including the term "flake" in

Appendix F, Part 3 Poisons (other than agricultural and veterinary chemicals) to be labelled with warning statements or safety directions.

- Members noted that the recommendation overlooked paragraph 17, this was, however, picked up and included. Members also noted that Paragraph 17 dealt with certain exemptions to labelling for camphor and naphthalene. Paragraph 28 provided for certain exemptions to container requirements for camphor and naphthalene. Paragraph 29 dealt with requirement for a device (for domestic use) which prevents removal or ingestion of naphthalene or camphor in ball, block, disc or pellet form. Industry and APVMA advice is needed to confirm Secretariat's opinion that some camphor products in flake form may be marketed.

· The steady flow of adverse experience reports related to naphthalene products indicated that there was a need to reconsider the existing scheduling and warning statements for naphthalene products, including their packaging and presentation, to further mitigate public health risk.

- Members noted that there was no specific recommendation on the scheduling status of naphthalene; the evaluator left this entirely to the ACCS. This was the basis for flagging in the pre-meeting notice that more restrictive scheduling may be considered.

The evaluator also concluded that:

· The registration of naphthalene in free flake form was not considered appropriate as this form presented the greatest potential exposure both to users and 'bystander' children. The flake form and the likely use pattern (scattered freely) increased potential inhalational exposure (if only through the greater surface area of the flakes), as well as the possibility of oral exposure through ingestion and greater dermal exposure through contact with treated clothes, bedding and furniture**.**

· Inclusion of flakes in tamper-proof sachets (or similar device) would reduce the risk of oral ingestion and hence the overall risk. It was impossible to give an unequivocal statement of the dermal and inhalational risk posed by these products without studies on naphthalene vapour release from stored clothes/bedding when using this form of product.

APVMA Labelling Compliance

There were 12 Australian registered home domestic products using naphthalene as insecticidal fumigants. The warning statements found on the labels varied and did not always comply with the APVMA's FAISD Handbook. No claims were made in any case as to child resistant packaging. Members noted that the FAISD Handbook was a consolidation of the advice provided to the APVMA by XXXXX and was intended to provide guidance to these parties in the approval of labels.

Additionally FAISD safety directions for naphthalene include:

· *Poisonous if inhaled or swallowed*

- *Will irritate the eyes and skin*
- *Repeated exposures may cause allergic disorders*
- *Do not inhale vapour*
- *Avoid contact with the eyes and skin*
- *Wash hands after use*

In the FAISD Handbook, naphthalene ("for domestic use, all forms") also has warning statements:

- *can be fatal to children if sucked or swallowed.*
- *do not use on the bedding or clothing of infants or in the bedrooms of young children 3 years of age or less.*

International Regulations

Members also noted the following conclusions from recent international assessments as summarised in the XXXXX report:

- Recent reviews by the United States Environmental Protection Authority (US EPA) (2008), the Canadian Pest Management Regulatory Agency (PMRA) (2010) and the European Chemicals Bureau (2003) have not supported the use of loose or flaked forms of naphthalene.
- The US EPA will not permit the marketing of loose mothballs from 2013, the PMRA has restricted naphthalene presentation to packaging that reduces the possibility for ingestion; this requires the containerization of flakes and loose mothballs.
- Loose mothballs and flakes of naphthalene have not been available in the EU since mid 2009 when approval was withdrawn following a lack of commercial interest by manufacturers in funding new studies to support the chemical in a European review of biocide products.

Main Concern

G6PD deficiency is reportedly present in about five per cent of Australians, mainly those of Asian, African, Middle Eastern or Mediterranean descent. This enzyme deficiency makes affected individuals liable to red cell haemolysis following naphthalene exposure. Haemolysis, whether due to chemical exposure or underlying pathological processes, leads to the production of bilirubin (as a breakdown product of haemoglobin from the lysed red cells) which causes jaundice. In adults and older children, jaundice is relatively harmless in itself. However, if this process occurs in the foetus or infant when the blood brain barrier is not fully formed, some of this bilirubin enters the brain and is deposited in cell bodies (grey matter), especially the basal ganglia, causing irreversible damage. Depending on the level of exposure, the effects range from clinically unnoticeable to

severe brain damage and even death. In severe cases of haemolysis there can also be serious kidney and liver damage resulting from precipitated haemoglobin.

Toxicology

Members noted the following toxicology summary for naphthalene (from a 2003 XXXXX evaluation, as no new toxicology data had been evaluated in the current XXXXX report):

XXXXX

- XXXXX naphthalene has low oral and dermal toxicity XXXXX but has moderate inhalational toxicity XXXXX. XXXXX are more sensitive to naphthalene with an oral LD_{50} reported in the range XXXXX.
- In XXXXX naphthalene is a slight eye and skin irritant. Naphthalene was not a skin sensitiser in a number of XXXXX studies using either the XXXXX. However, in sensitised individual persons naphthalene produces severe dermatitis and is a skin irritant.
  - Members also noted that a more recent (September 2008) United States Environmental Protection Agency's Re-registration Eligibility Decision for Naphthalene Report (US EPA Report) (accessible at www.epa.gov/opp00001/reregistration/REDs/naphthalene-red.pdf) indicated that naphthalene was a slight to moderate eye irritant and moderate skin irritant in rats.
- The lowest lethal doses reported in humans were 100 mg/kg bw in a child and 29 mg/kg and 74 mg/kg in adults. Occupational ocular exposure to naphthalene dust had been reported to cause corneal irritation and injury, with cataracts forming after prolonged exposure.
- The evaluator asserted that although naphthalene had low to moderate acute oral toxicity and moderate inhalation toxicity, deaths in humans had been reported after quite low oral exposures of the order of 100 mg/kg bw or less and anaemia in infants had been associated with dermal/inhalational exposure.

Members additionally noted the following from the US EPA report.

Toxicological Doses and Endpoints for Naphthalene for Use in Human Health Risk Assessments	
Exposure	**Study and Toxicological Effects**
Dermal (Short-Term; 1-30 d)	90-d Dermal Toxicity Study –Rat NOAEL = 300 mg/kg/d. LOAEL = 1000 mg/kg/d based on atrophy of seminiferous tubules in males, and nonneoplastic lesions in the cervical lymph node (hyperplasia), liver (haemosiderosis), thyroid thyroglossal duct cysts, kidneys (pyelonephritis), urinary bladder (hyperplasia) and skin (acanthosis, hyperkeratosis) in females.
Inhalation (Intermediate-term; 1-6 months)	13-Week (nose-only) Inhalation Rat Study; Subchronic (nose-only) Neurotoxicity Rat Study NOAEL = 5.2 mg/m^3 (Subchronic neurotoxicity study) NOAEL (13 week inhalation study) – not identified. LOAEL = 10 mg/m^3 (13 week inhalation study) based on increased incidence and severity of nasal lesions (degeneration, atrophy and hyperplasia of basal cells of the olfactory epithelium; rosette formation of olfactory epithelium; loss of Bowman's glands; hypertrophy of respiratory epithelium). LOAEL = 10 ppm (subchronic neurotoxicity study) based on atrophy/disorganization of the olfactory epithelium and hyperplasia of the respiratory and transitional epithelium.
Inhalation (Long-term; > 6 months)	National Toxicology Program Chronic Toxicity and Carcinogenicity Studies in the Rat and Mouse NOAEL = not identified LOAEL (rat study) = 52 mg/m^3 based on increased incidence and severity of atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia.

Genotoxicity

- A number of bacterial reverse mutation assays have been conducted with naphthalene in strains of XXXXX which all gave negative results. In the presence of XXXXX chromosome aberrations were produced by naphthalene in XXXXX and sister chromatid exchanges (SCEs) were produced in these cells both in the presence and absence of XXXXX. Also noted two micronucleus assays in the literature which recorded positive results, an SCE assay in human lymphocytes + XXXXX which was negative, and a positive result in a *Drosophila melanogaster* XXXXX and recombination test and a small dose related increase in micronucleated erythrocytes in salamanders exposed for 12 d.
- The evaluator asserted that overall the genotoxicity of naphthalene was equivocal. The *in vitro* studies which used the normal microsomal preparations from XXXXX should be interpreted cautiously as the XXXXX may have lacked biologically significant levels of the CYP2F2 isozyme of cytochrome P450. This enzyme is selectively expressed in lung and respiratory epithelial tissues.

Human carcinogenicity

- The 2002 International Agency for Research on Cancer (IARC 2002 Report) (accessible at www.inchem.org/documents/iarc/vol82/82-06.html) concluded that "there is inadequate evidence in humans for the carcinogenicity of naphthalene. There is sufficient evidence in experimental animals for the carcinogenicity of naphthalene. The overall evaluation is that naphthalene is possibly carcinogenic to

humans (Group 2B). Whilst the evidence for carcinogenicity in rodents is convincing, the relevance to humans at likely domestic exposure levels is questionable as the available evidence points to a considerably lower susceptibility of humans than of rodents. Tumours in rodents occurred in tissues especially prone to naphthalene injury, (hyperplasia, inflammation and/or necrosis), when exposure was by either the inhalation or the intraperitoneal (ip) route".

- The evaluator further indicated that US National Toxicology Program 2005 studies noted that the metabolism of naphthalene at the upper exposure levels was saturated, leading to maximal production of the reactive epoxide and therefore maximal demand on the glutathione conjugation pathway. Toxicokinetic and anatomic differences render the rat and mouse considerably more sensitive than primates to carcinogenesis resulting from inhalational exposure.
- The evaluator noted that although only a LOEL and not a NOEL was established for tumours in XXXXX at the doses tested, the available data indicated that:
  - the public were generally exposed to naphthalene in the home at levels approximately 3 orders of magnitude lower than the lowest exposure level used in the XXXXX;
  - rates of metabolic activation to form the likely carcinogen in exposed tissues were approximately 2 orders of magnitude lower than in XXXXX; and
  - that the potential for glutathione depletion (other than in the red blood cells of G6PD individuals) was far lower in humans than in XXXXX due to an alternative metabolic pathway predominating in humans.
- The evaluator concluded that on this basis the use of naphthalene products was not likely to pose a risk of carcinogenesis in humans exposed in the domestic environment.

Members additionally noted the following relevant carcinogenic information in the 2008 US EPA report:

- Results from chronic studies show that carcinogenic effects have been observed in both rats and mice following inhalation exposure to naphthalene. In the rat, nasal tumours included neuroblastomas of the olfactory epithelium and adenomas of the respiratory epithelium. There was also an increase in the incidences of adenoma of the respiratory epithelium.
- The report concluded that "under the conditions of this 2-year inhalation study, there was clear evidence of carcinogenic activity of naphthalene in male and female rats based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose."
- In the mouse study, male mice had statistically significant increased incidences of liver adenomas, and adenomas and carcinomas combined. Female mice exhibited

increased incidences of alveolar/bronchiolar adenomas, and adenomas and carcinomas combined.

- The US EPA report concluded that "under the conditions of this 2-yr inhalation study, there was no evidence of carcinogenic activity" of naphthalene in male mice exposed to 10 or 30 ppm. There was "some evidence of carcinogenic activity" of naphthalene in female mice, based on increased incidences of pulmonary alveolar/bronchiolar adenomas.
- The US EPA report also advised that the carcinogenic potential of naphthalene was currently undergoing review and when this review was finalised the EPA would determine whether the human health hazard potential of naphthalene warranted revisiting.

Human Incident Data

- The XXXXX report also reiterated the case reports of naphthalene poisoning that were provided to the NDPSC in 2003. The evaluator advised that this data (see table below) did not include recent information from the Australian PIC.

Exposure	**Subject Age**	**Outcome**[#]
Oral Exposures		
Oral, "part of a mothball" (notes 34 cases of poisoning by ingestion)	21 months	acute haemolytic anaemia resolving after several transfusions – African American, Canada
Ingestion of 1 or more mothballs	2 yr	haemolytic anaemia, survived, - race not given, USA
Ingestion of half a mothball	17 months	haemolytic anaemia, survived - African American, USA
Ingestion of one mothball	6 yr	haemolytic anaemia, survived - Indian, India
Ingestion of 1 or more mothballs	2 yr, 2 yr 2.5 yr, 2.25 yr	haemolytic anaemia, all survived, - African American, USA
Ingestion of mothballs/flakes, (7 cases) Playing where naphthalene products were available (5), wearing treated clothing (2)	1.5-39 months (mean 23 months)	haemolytic anaemia, all survived - USA
Inhalation/dermal - children		
"Very small amounts in diapers"	"infants"	haemolytic anaemia - Canada
Primarily by inhalation from clothes, blankets, diapers etc. Cases occurred in autumn/winter from bedding/clothing stored with mothballs. In many cases no skin contact occurred.	0-39 d	haemolytic anemia, 2 deaths, not all cases were G6PD deficient (9 with normal values), - Greek, Greece
Diapers stored with mothballs, rinsed before use but still smelt of mothballs	6 d	Died from haemolytic anaemia - NOT Greek, Italian or other genetically predisposed population, USA
Naphthalene impregnated clothing	14 d, 9 d	Haemolytic anaemia, survived. Both G6PD deficient - African American, USA
Naphthalene impregnated clothing	11 d	haemolytic anaemia, survived - Chinese, USA
Naphthalene impregnated clothing	47 d	twins, haemolytic anaemia, survived - Greek, Australia

Exposure	Subject Age	Outcome[#]
Oral Exposures		
Inhalation/Dermal - adults		
Naphthalene treated blankets	young adult males (army recruits)	6 cases of severe haemolysis, 1 of which was fatal - Greek, Greece

[#] In almost all cases treatment consisted of blood transfusions.

Previous Scheduling Considerations

February 2004

- In February 2004 the NDPSC considered naphthalene, including several case reports of naphthalene poisoning via differing exposure routes (mostly from overseas) and confirmed that the Schedule 6 entry was appropriate and that a new warning statement should be included in Appendix F, Part 1. This warning statement (105) was identical to the wording of the FAISD statement 44. The NDPSC concluded that this statement should be a requirement for naphthalene products to alert users to the potential hazard that naphthalene presents to young children.

June 2006

- In 2006 the NDPSC again considered naphthalene in light of an Australian report of haemolytic anaemia in a child exposed to naphthalene. In this case, flakes had apparently been used in the storage of furniture, including the baby's cot. The NDPSC reconfirmed that the Schedule 6 entry was appropriate and that warning statement 105 should remain a requirement for naphthalene products to alert users to the potential hazard that naphthalene presents to young children.
    - ACCS Members recalled that Appendix F (Warning Statements and Safety Directions) no longer applied to agricultural and veterinary chemicals registered by the APVMA i.e. this was set entirely through the APVMA's product approach process, with the FAISD providing guidance on labelling for this process.

Other information

Members noted the following human incidents from the 2008 US EPA's report for the period of 1993 to 2005:

- Naphthalene produced a disproportionately high number of exposure incidents when compared to the composite average of exposure incidents reported for all other pesticides. This pattern observed in the combined population (occupational, non-occupational, children) was largely due to the frequency of reported incidents among children less than 6 yr.
- Exposure to children was much higher than a typical pesticide. This may be attributed to the widespread use of naphthalene products in homes and the ease of accessing the product as it was applied as loose mothballs.

- Naphthalene data show average results of about 1647 exposures per year, 133 symptomatic cases per year, and 310 cases per year seen in a heath care facility.
- No apparent annual trend was evident in the 13 year-span of data collected, as the number of reported incidents/year has remained relatively stable.
- Data indicated that indoor uses of naphthalene were responsible for a large number of cases.
- The large majority of incidents for children under 6 yr of age were from ingestion of mothball products used indoors.
- From a 13-year period of data, approximately seven per cent of naphthalene incidents in children resulted in any symptoms at all, and less than one per cent had moderate or major symptoms. Symptoms that did occur (both adults and children; all routes of exposure) were not life-threatening and include nausea, vomiting, headache, dizziness, drowsiness/lethargy, eye irritation, respiratory irritation, and dermal oedema and erythema.

Members also noted the following from the Californian Environmental Protection Agency's Chronic Toxicity Summary report (accessible at http://oehha.ca.gov/air/chronic_rels/pdf/91203.pdf):

- Nine persons (eight adults and one child) were exposed to naphthalene vapours from several hundred mothballs in their homes. Nausea, vomiting, abdominal pain, and anaemia were reported. Testing at one home following the incident indicated an airborne naphthalene concentration of 20 ppb (105 µg/m^3). Symptoms abated after removal of the mothballs.
- Ingestion of naphthalene or p-dichlorobenzene mothballs was a frequent cause of accidental poisoning of children. Infants exposed to naphthalene vapours from clothes or blankets have become ill or have died. The effects in infants have been associated with maternal naphthalene exposure during gestation.
- Deaths have been reported following ingestion of naphthalene mothballs. A 17-yr old male who ingested mothballs developed gastrointestinal bleeding, haematuria, and coma, and died after five days. A 30-yr old female ingested 30 mothballs and died after five days.
- Acute haemolytic anaemia was reported among 21 infants exposed to naphthalene vapours from nearby mothball-treated materials. Increased serum bilirubin, methaemoglobin, Heinz bodies, and fragmented red blood cells were observed. Kernicterus was noted in eight of the children, and two of the children died. Ten of these children were G6PD deficient.
- A 12-yr old male ingested 4 g of naphthalene and 20 h later developed haematuria, anaemia, restlessness and liver enlargement. The patient recovered after 8 d.
- A 69-yr old female developed aplastic anaemia two months after several weeks of exposure to naphthalene and p-dichlorobenzene.

- Workers occupationally exposed to naphthalene fumes or dust for up to five years were studied for adverse ocular effects. Multiple pin-point opacities developed in 8 of 21 workers. Vision did not appear to be impaired. Cataracts and retinal haemorrhage were observed in a 44 yr old man occupationally exposed to powdered naphthalene, and a co-worker developed chorioretinitis.
- Majority of 15 persons involved in naphthalene manufacture developed either rhinopharyngolaryngitis and/or laryngeal carcinoma.

Hazard Classification

- Members noted that naphthalene was listed in Safe Work Australia's Hazardous Substances Information Systems (HSIS) as a Category 3 carcinogen with a risk phrase: *"R40 Limited evidence of a carcinogenic effect and as harmful by the oral route"*.

June 2011 Pre-meeting Submissions

XXXXX noted that the haemolytic episodes in adults and older children were usually brief, because the body continues to produce red blood cells, and was therefore relatively harmless. The submission further stated that haemolytic episodes could be triggered by various factors, such as stress, infection and certain chemicals including naphthalene. The following issues were raised:

- Recent concerns over the risks posed by naphthalene on new born babies with G6PD were already considered at the October 2003, February 2004 and June 2006 NDPSC meetings and various controls were applied. Asserted that these controls were considered appropriate.
- International considerations of naphthalene have focused on the ingestion hazard for young children as the main hazard of concern.
- The US EPA in 2008 determined that products containing naphthalene were eligible for re-registration provided that specific label amendments were made. Members noted that the US EPA report indicates that all indoor moth repellent products should contain the following label warning statement "**Keep out of reach of children**. Do not place in areas accessible to children". Limitations were also placed on the physical form of naphthalene to be supplied to discourage children consuming the product.
- The US EPA report concluded that inhalation did not represent a risk of concern. The carcinogenic potential of naphthalene resulting from inhalation exposure was being assessed.
- Health Canada called for further mitigation through child-resistant packaging to reduce ingestion risk.

The submission also provided specific arguments on the following three issues:

Ingestion risk

- Noted that currently only the flake form for domestic use did not require a tamper proof container. Argued that due to its smaller size and lesser appeal, flakes may be less likely to be picked up and ingested by young children. Due to their convenient size, mothballs, blocks and cakes were more likely to be picked up and ingested by young children. Asserted that XXXXX only supplied naphthalene flakes for household use and no incidents had been reported.
- Noted that the US EPA and Health Canada's consideration of the ingestion risk for naphthalene had focused on the naphthalene size as an indicator for ingestion risk by children. Although both countries have indicated that no special packaging requirement was needed for large blocks or cakes (approximately 7 cm diameter), loose mothballs, including flakes, were required to be packed in special packaging.
- Requested that the risk mitigation consideration of the Committee be consistently aligned with the likelihood of ingestion by children. Indicated that if the Committee believed that the size of naphthalene was the key to determining the level of ingestion risk, then the scheduling consideration should be aligned with the US EPA and Health Canada. If the consideration of ingestion risk was based on the appeal to young children and the ease with which the naphthalene could be picked up, then the current scheduling requirements were appropriate.
- Indicated that if the Committee considered that the ingestion risk for young children for naphthalene flakes was equal to or greater than ingestion risk for mothballs, blocks, discs or pellets, packaging changes may be required. The submission therefore requested that a minimum period of two years be allocated to implement such a change, consistent with the US EPA's implementation date (September 2013).

Risks for G6PD individuals

- Noted that in 2004 and 2006 the NDPSC considered the risks to the G6PD individuals and since then no new information had emerged.
- Agreed that although the risks posed by naphthalene to new born babies and young children with G6PD were high, naphthalene was neither the cause of the G6PD nor the only trigger for a haemolytic crisis in G6PD individuals.
- Noted that there were products registered with APVMA that did not display relevant warning statements, particularly statement 105 and Appendix F, and these issues should be addressed.
- Noted that amendments to existing labels ensuring that naphthalene was not used in bedding or clothing of infants and children were best done through APVMA. This should address the risks for G6PD deficient infants.

Other uses of naphthalene

- Indicated that naphthalene as an impurity existed in many hydrocarbon solvents, including kerosene, diesel, mineral turpentine and light mineral oils. Members noted that the submission did not provide details of the impurity levels.
- The hydrocarbon solvent parent entry was in Schedule 5 and naphthalene parent entry was in Schedule 6, with no specific exemptions for impurities or cut-off levels provided. Members noted that a low concentration cut-off to exempt of 1 mg/kg for naphthalene through the Appendix G entry had been in place since May 1992.
- Asserted that the risk posed by naphthalene as an impurity in hydrocarbon solvents was not a regulatory concern. The submission requested that the Committee consider exempting naphthalene when present in hydrocarbon solvents as an impurity. Members noted that no data or suggestions were provided regarding any upper limit on this requested exemption.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that 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) formulation, labelling, packaging and presentation of a substance.

A Member argued that the main reasons for naphthalene poisoning were due to its entrenched use as a common household pesticide and easy availability from retail outlets. Consequently, the public perceived that naphthalene was a safe product and did not heed the label warnings. Other Members agreed, but asserted that scheduling was not an appropriate instrument for changing these attitudes. This issue is further discussed under the "Non-scheduling actions" section below.

Several Members asserted that, while scheduling may not be the best way to change entrenched use patterns for these products, there still remained specific risks identified by the evaluator, i.e. oral ingestion and inhalation, which could be addressed through scheduling. In this regard a Member argued that mothballs were more attractive to children than flakes and had a greater risk of being picked-up and consumed. The Committee, however, agreed that as flakes were scattered liberally in bedrooms and wardrobes, they were also easily accessible to children and equally hazardous. A Member further indicated that due to their larger surface area, flakes vaporise more rapidly compared to other naphthalene forms. The Member noted results from a study conducted to measure the indoor volatile potential of naphthalene indicated that higher concentrations of naphthalene were released into the atmosphere from flakes than from balls or blocks.

Several Members noted, however, that although hazards and risks associated with naphthalene flakes were consistent with other naphthalene forms, naphthalene flakes were not currently required to be supplied in the tamper proof packaging as were other naphthalene forms. The Members therefore agreed that appropriate tamper proof

packaging was necessary for naphthalene flakes and decided to recommend that flakes be included in the SUSMP Part 2, paragraph 29, along with other naphthalene forms. Members also noted that paragraph 29 in effect created a permanent immediate container. It was agreed that, similar to other forms of naphthalene and camphor, only limited labelling and packaging requirements achieved through SUSMP Part 2 (paragraph 17 and 28) were necessary for flakes packaged as per paragraph 29. Members therefore agreed to recommend inclusion of the flake form in paragraph 17 and paragraph 28.

Members also noted the APVMA's June 2011 restrictions on naphthalene flakes and discussed whether a scheduling ban, in line with APVMA's action, should be imposed by including flakes in Appendix C or Schedule 7. A Member noted that a PIC had been receiving one call per week regarding naphthalene poisonings. Another Member indicated that another PIC reported similar rates (45 to 65 naphthalene incidence calls per year in the last five years) and argued that inclusion of flakes in Appendix C would be appropriate as this would restrict the availability and subsequent naphthalene poisoning. Several Members, however, argued that no new toxicology data had been presented with the current application, and the previous NDPSC decision on the broad naphthalene scheduling remained appropriate. A Member suggested that the poisoning risks could better be addressed via the APVMA regulatory process, i.e. packaging, appropriate labelling and tamper proof containers, compliance process and public awareness campaigns.

Non-scheduling actions

Several Members argued that appropriate label warnings and packaging alone were insufficient to prevent naphthalene poisoning and public education and an efficient compliance system were also equally essential. Some Members indicated that the current compliance with the APVMA's FAISD was inadequate and this had potentially contributed to the recent adverse incidents. Members therefore recommended that the delegate should refer this concern to the APVMA.

As a separate issue, a Member noted that as toilet deodorant blocks also contain naphthalene, label warning statements and tamper proof packaging, similar to other naphthalene forms, was required. Another Member noted that the active ingredient in the toilet deodorant block was not usually naphthalene but other substances, including paradichlorobenzene. The Committee agreed that the toilet deodorant blocks were not for domestic use and exposure and hazards scenarios were different from the domestic naphthalene use, therefore this was not a concern.

Other matters

Impurity in hydrocarbons

A Member supported one pre-meeting submission's claim that the Schedule 6 parent entry for naphthalene would inadvertently capture various hydrocarbon solvents that contain naphthalene as an impurity. The Member further argued that this was not a

regulatory concern and that it would be appropriate to specifically exempt this from scheduling. Another Member contended, however, that to consider such a request, data on naphthalene levels present in these hydrocarbon solvents would be required. Other Members responded that naphthalene impurities were an inevitable component of hydrocarbon solvents. The Committee generally agreed that the Schedule 5 listing for liquid hydrocarbons with specific controls, including child-resistant closures, was sufficient to mitigate any risks from naphthalene impurities in these products. Members therefore agreed to add an exemption to the Schedule 6 naphthalene parent entry to exclude naphthalene in liquid hydrocarbons as an impurity.

Appendix F

A Member questioned whether inclusion of naphthalene flakes in Appendix F was required, noting that Appendix F label warning statements and safety directions were no longer required for pesticides registered by the APVMA. The Committee generally agreed that although Appendix F statements were not compulsory for pesticides registered by the APVMA, other naphthalene and camphor forms had already been included in Appendix F. Therefore Members agreed that, for consistency, naphthalene flakes should also be included in Appendix F.

Implementation period

A Member argued for a long implementation period (at least 22 months) for labelling changes (i.e. but not for the hydrocarbon solvents exemption) stating that there was likely to be a large number of existing stock and that labelling and repackaging would take some time. Several Members argued for no delay as this labelling and packaging change for flakes was due to risk concerns and there would be no regulatory impact as APVMA had already placed restrictions on the sale of naphthalene flakes. The Committee did not support an extended implementation period, but did agree that this should be at least 6 months.

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 acknowledged that the human health safety issue of naphthalene flakes was of concern and this issue can be addressed via labelling and packaging requirements similar to that of other naphthalene forms, such as blocks, balls and pellets. The delegate therefore decided to include naphthalene flakes in Part 2, Paragraph 17, 28 and 29 of the SUSMP. Furthermore, the delegate also decided to include naphthalene flake forms in Appendix F. The delegate also noted that, as an urgent safety issue, an early implementation period i.e. January 2012 was necessary and this early implementation period would not unduly disadvantage the affected industries.

The delegate noted that the proposed amendments for naphthalene flakes would capture camphor flake forms as well. Consequently, industries that produce camphor flake forms would have to satisfy the proposed labelling and packaging requirements similar to that of naphthalene flake forms. The delegate indicated that as the human toxicology potential of camphor flakes was not considered, if the affected industries raised this issue this matter could then be further considered.

The delegate noted that despite the lack of information regarding a suitable concentration cut-off to exempt naphthalene present in liquid hydrocarbons as an impurity, the proposed Schedule 6 amendment to exempt all strengths and concentrations of naphthalene impurity was supported. This amendment would serve as an interim measure to avoid any unintended regulatory consequences.

The delegate agreed that 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) formulation, labelling, packaging and presentation of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include the term "flake" in SUSMP Part 2 Labels and Containers paragraphs 17, 28 and 29. Additionally, the delegate decided to include the term "flake" in the Appendix F, Part 3 entries for camphor and naphthalene. The delegate further decided that the existing Schedule 6 naphthalene entry be amended to exclude liquid hydrocarbons as an impurity.

The delegate decided an implementation date of 1 January 2012 (i.e. three months after publication of the final decision).

The delegate also agreed to refer ACCS's concern regarding FAISD compliance issues to APVMA.

SUBMISSIONS ON DELEGATE'S INTERIM DECISION

XXXXX submitted a public submission on the delegate's interim decision. The submission supported the delegate's interim decision to exempt naphthalene when present as an impurity in hydrocarbon solvents from scheduling.

The submission also made several points, as summarised below:

- Noted that the ACCS agreed that hazards and risks associated with naphthalene flakes were consistent with other naphthalene forms and therefore recommended naphthalene flakes be added to Paragraphs 17, 28 and 29 of the SUSMP.
- Argued that as naphthalene works by releasing vapours, therefore inhalation risk of naphthalene flakes would be unlikely to change regardless of whether they were provided in free flake form or in an enclosed device.

- Indicated that it assumes the decision to allow flakes to be supplied in an enclosed device was based on the consideration that picking up and/or sucking on an enclosed device containing naphthalene flake was likely to deliver a lower dose of naphthalene than picking up and/or ingesting free flake forms of naphthalene.
- Sought clarification on ACCS's recommendation and the delegate's interim decision to include naphthalene flake forms in paragraphs 17, 28 and 29 and resulting packaging and labelling requirements. Noted that clarification would assist the affected industries in planning the necessary risk mitigation measures to address risk concerns.
- Argued that naphthalene flakes were much smaller in size than naphthalene balls, discs and blocks, and therefore could not be provided in cages i.e. tamper proof containers. Noted that the only possible option was to consider a see-through sachet-like enclosure where naphthalene vapour can escape, but the flakes themselves would be contained. Sought clarification whether these individual sachets were acceptable and would also need to have the word POISON and naphthalene embossed or indelibly printed on them.
- Further noted that it believed that these additional labelling requirements were not imposed internationally.

DELEGATE'S FINAL DISCUSSION

The delegate considered the submission received in response to the interim decision and noted that:

- The submission requested the delegate's clarification on some aspects of packaging and labelling requirements for naphthalene flakes. The delegate noted that SUSMP Part 2 Paragraph 28 would require naphthalene flakes sachets to bear the word POISON and the active ingredient's name.
- The submission also requested the delegate's clarification on whether a "see-through sachet" for naphthalene flakes would meet the packaging requirement. The delegate indicated that such packaging requirements were of a regulatory rather than scheduling nature and these would be addressed during the product approval process.
- The submission noted that this assumed that picking up and/or sucking on an enclosed device containing naphthalene flake was likely to deliver a lower dose of naphthalene than picking up and/or ingesting free flake forms of naphthalene. The delegate noted that this issue was not discussed at the meeting. The delegate also noted, however, that the Committee agreed that hazards and risks associated with naphthalene flakes were consistent with other naphthalene forms. Based on this the Committee recommended, and the delegate agreed, that appropriate tamper proof packaging was necessary for naphthalene flake forms.

The delegate, however, noted that Part 2 Paragraph 28 indicates that the packaging should, in normal use, prevent removal or ingestion of its contents. The delegate made

the distinction between this interpretation and requirements for "non-access packaging" as covered by the Australian Standard AS 4710-2001 (*Packages for chemicals not intended for access or contact with their contents by humans*) requirements. This Standard claims "This Standard specifies requirements for packages for chemicals, designed to be non-accessible to human beings. Additionally, it specifies requirements for packaging systems which are designed to prevent unintended contact with the contents of the package."

DELEGATE'S FINAL DECISION

The delegate decided to include the term "flake" in SUSMP Part 2 Labels and Containers paragraphs 17, 28 and 29. Additionally, the delegate decided to include the term "flake" in the Appendix F, Part 3 entries for camphor and naphthalene. The delegate further decided that the existing Schedule 6 naphthalene entry be amended to exclude liquid hydrocarbons as an impurity.

The delegate decided an implementation date of 1 January 2012 (i.e. three months after publication of the final decision).

The delegate also agreed to refer ACCS's concern regarding FAISD compliance issues to APVMA.

Part 2, Paragraph 17 – Amendment

Part 2, Paragraph 17 – Amend entry to read:

Camphor and naphthalene

17. The labelling requirements of sub-paragraph 3(4) and paragraph 7 do not apply to a device that contains camphor or naphthalene in block, ball, disc, pellet or flake form if the device:

    (1) complies with paragraph 28; and

    (2) is sold or supplied in a primary pack labelled in accordance with paragraphs 3 and 7.

Part 2, Paragraph 28 – Amend entry to read:

Camphor and naphthalene

28. The container requirements of paragraph 21 do not apply to a device that contains only camphor or naphthalene in block, ball, disc, pellet or flake form for domestic use, if the device:

    (1) in normal use, prevents removal or ingestion of its contents; and

(2) is incapable of reacting with the poison; and

(3) is sufficiently strong to withstand the ordinary risks of handling, storage or transport; and

(4) has the word "POISON" and the approved name of the poison embossed or indelibly printed on it.

Part 2, paragraph 29 – Amend entry to read:

Prohibitions

29. A person must not sell or supply camphor or naphthalene in ball, block, disc, pellet or flake form for domestic use unless the balls, blocks, discs, pellets or flakes are enclosed in a device which prevents removal or ingestion of its contents.

Schedule 6 – Amendment

NAPHTHALENE – Amend entry to read:

NAPHTHALENE (excluding its derivatives) **except** in liquid hydrocarbons as an impurity.

APPENDIX F, PART 3 – Amendment

Camphor – Amend entry to read:

POISON		**SAFETY DIRECTIONS**	**WARNING STATEMENTS**
Camphor			
(a)	in block, ball, disc, pellet or flake form, enclosed in a device which, in normal use, prevents removal or ingestion of its contents.	9	
(b)	in other forms	9	1

Naphthalene			
(a)	in block, ball, disc, pellet or flake form, enclosed in a device which, in normal use, prevents removal or ingestion of its contents.	9, 105	
(b)	in other forms	9, 105	1

2. MATTERS INITIALLY REFERRED TO ACMS#3 – JUNE 2011

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

2.1.1 LOPERAMIDE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

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

Loperamide – proposal to reschedule loperamide in packs of eight dosage units or less, up to a maximum of one days' supply, from Schedule 2 to unscheduled.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended exempting loperamide in divided preparations for oral use containing not more than 2 mg of loperamide in packs of 8 dosage units or less. The Committee recommended an implementation date of at least 6 months after the delegate's final decision (earliest 1 May 2012).

The Committee also recommended that the delegate communicate the evaluator's labelling recommendations to the appropriate area within the TGA.

BACKGROUND

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions. It is given orally as an antidiarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the management of colostomies or ileostomies to reduce the volume of discharge. Available anti-diarrhoeal OTC treatments include loperamide, loperamide+simethicone combination, diphenoxylate / atropine, adsorbents (kaolin and pectin) and probiotics.

Loperamide was first considered by the NDPSC in November 1978. The NDPSC decided to include loperamide in Schedule 4.

In May 1983, the NDPSC considered an application for the rescheduling of loperamide 2 mg capsules for a maximum of 2 – 3 days supply for use in chronic diarrhoea from Schedule 4 to Schedule 3. The NDPSC did not support the proposed down-scheduling due to concerns over the possible risks associated with the early use of loperamide and its suitability as an over-the-counter (OTC) substance.

In August 1986, the NDPSC again considered an application to down-schedule loperamide. The application was considered to be more comprehensive than the 1983

application and the NDPSC agreed to reschedule loperamide 2 mg in pack of 8 capsules to Schedule 3 with a new Appendix F warning statement. This decision was confirmed in November 1986.

In August 1996, the NDPSC considered an application to down-schedule loperamide in packs of 8 dosage units, each dosage unit containing 2 mg or less of loperamide, from Schedule 3 to Schedule 2. The NDPSC did not support the request due to the need for professional advice at the point of sale and the potential risks associated with more widespread use.

In February 2000, the Trans-Tasman Harmonisation Working Party recommended removal of the current dose and pack size restrictions for loperamide from Schedule 2 and include loperamide when given by injection in Schedule 4. In August 2000, the NDPSC agreed to harmonise with New Zealand and increased the Schedule 2 pack size limit of loperamide from 8 dosage units to a maximum of 20 dosage units.

In June 2009, the NDPSC decided to amend the current Schedule 2 entry for loperamide to include the word 'divided' to further clarify that liquid preparations were captured by Schedule 4.

In June 2010, the NDPSC did not support an application to exempt loperamide for oral use, when in a maximum pack size of 8 dosage units, with each dosage unit containing 2 mg or less of loperamide. The NDPSC's discussion at the June 2010 meeting is summarised below, under the Submissions heading.

XXXXX submitted an application direct to the Scheduling Secretariat again seeking the above exemption for loperamide. A delegate agreed that this was a matter warranting advice from the ACMS and referred this to the June 2011 ACMS meeting.

SCHEDULING STATUS

Loperamide is listed in Schedule 2 for divided preparations for oral use in packs of 20 dosage units or less. All other preparations are captured by Schedule 4.

Loperamide when in Schedule 2 is also listed in Appendix F with a requirement for labelling with warning statement 41 ("*Do not use beyond 48 hours*"). However, the requirements for labelling of OTC medicines have now been transferred into the TGA's *Required Advisory Statements for Medicine Labels* (RASML).

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX requested an exemption from scheduling for loperamide for oral use, when in a maximum pack size of 8 dosage units (one days' supply), with each dosage unit containing 2 mg or less of loperamide. The application also noted that the proposed

rescheduling would harmonise with the scheduling of loperamide in New Zealand. The application made the following general points:

- Stated that loperamide was a safe and effective treatment for adults and children over 12 years of age with acute diarrhoea. Stated that acute diarrhoea in the Western world was usually a benign condition and a common illness amongst adults where episodes were generally brief and self limiting.
- Stated that the symptoms of acute diarrhoea were generally of a quick onset and could occur at any time and cause debilitating and socially distressing symptoms. Asserted that due to the self evident urgency of a bout of diarrhoea, availability of effective control with a good safety profile was of clear community benefit.
- Asserted that withholding treatment of symptoms with loperamide in the absence of warning signs would be unnecessary and would only exacerbate the distress of the disorder.
- Noted that high risk groups include babies and children (for which this substance was not recommended) and the elderly who were already likely to be under medical supervision.
- Asserted that overall the adverse event profile of loperamide demonstrated that it was a well tolerated drug and most reported adverse events were mild to moderate in nature.

The application also included a copy of the evaluation report on the June 2010 application which supported the proposed rescheduling. Many of the points from the 2010 application and evaluation report were reiterated in the 2011 application and evaluation and have been included in the sections following.

Following the June 2010 NDPSC decision not to reschedule loperamide, the applicant approached three gastroenterologists to provide expert comment on the objections raised in the Record of Reasons. These experts supported the proposed exemption for loperamide, provided that adequate patient information was included with the product packaging. The details of the expert opinions are summarised below:

- Asserted that the availability of a pharmacist was not essential for short term OTC loperamide. Stated that loperamide had a high safety profile with a long track record of safe use and little likelihood of clinically significant adverse events. Asserted that it was safer relative to other unscheduled products such as NSAIDS, aspirin and paracetamol.
- Stated that loperamide had been available in grocery stores in the UK and USA for many years without any significant post marketing surveillance concerns and it would seem appropriate for its availability to be the same in Australia.
- Agreed that maintaining hydration was the cornerstone of therapy for acute diarrhoea, noting that neither loperamide nor hydration treats the underlying cause of diarrhoea. Noted also that in the majority of adults with acute diarrhoea in the Australian

community, dehydration did not occur. Asserted that the major impact was instead the inconvenience of frequent loose stools associated with loss of productivity and quality of life. Asserted that loperamide, in this context, was an important short term therapy to control acute diarrhoea. Asserted that loperamide was both a primary and supportive treatment for diarrhoea and a useful adjunct to (but not a substitute for) adequate hydration.

- Stated that there was no signal in post marketing surveillance over 30 years indicating that abuse/misuse was a problem. Based on the pharmacology of the agent it was assessed to have a very low abuse potential. Asserted that small pack size and cost were mitigators of inappropriate use or abuse.
- Made the following suggestions for appropriate communication for the pack:
  - although the maximum recommended daily dose was 8 tablets, recommended inclusion of a statement informing consumers that a dose of 3 – 4 tablets was generally sufficient for a single bout of diarrhoea.
  - guidance on spacing of dosing so that people did not take multiple doses in quick succession before the initial dose has had time to work.
  - inclusion of 'severe (stomach) pain' and bloody diarrhoea as a caution to seek healthcare professional advice.
  - inclusion of a caution to 'maintain adequate hydration'.
- Asserted that clinically relevant drug interactions with short term use were not identified as a problem and current Schedule 2 packaging had been available for many years without the requirement of a CMI.
- Stated that in the context of the pharmaceuticals available in the unscheduled environment, loperamide was at the very low end of risk while being at the higher end of benefit and was suitable for general sale.

Other main points of the application addressing section 52E have been summarised as part of the evaluation report section.

Evaluation Report

The evaluator supported the proposed down-scheduling of loperamide from Schedule 2 to exempt when in a maximum pack size of 8 dosage units, each containing 2 mg or less of loperamide, provided that adequate patient information was included in the labelling or the packaging.

As the approval of labelling and packaging rests with the Therapeutic Goods Administration (TGA), the evaluator suggested that the following be brought to the TGA's attention:

- there was a need for greater specificity about which medications may interact with loperamide with clinical consequences. The advice needed to take into account likely

differences between short term use with the dosage schedule recommended for acute diarrhoea and use to treat chronic disease states;

- the labelling suggestions in the Expert Comment (see above) should be adopted for the exempt pack;
- an appropriate icon or warning should be used to contraindicate use in pregnancy;
- that the currency of the listing of adverse reactions in the product information be reviewed; and
- if necessary, a package insert should be required for the exempt pack. Consideration should also be given to whether a shorter document than the Consumer Medicine Information (CMI) would convey key messages.

The evaluator noted that there was a considerable overlap in the material submitted as part of the current and pre-June 2010 applications. The evaluator noted that the new material consisted of comment by three Australian specialist gastroenterologists approached by the sponsor to review the objections previously raised during the June 2010 NDPSC consideration, details of Australian adverse drug reaction reporting for loperamide and three additional references. The evaluator focussed on the application's aim to address matters raised in the NDPSC consideration, however also reiterated some comments made as part of the previous evaluation. A summary of the material provided and relevant evaluator comments is provided below:

(a) Risks and benefits

- Noted studies comparing the efficacy of loperamide with diphenoxylate/atropine in patients with acute diarrhoea; where less loperamide was needed to control diarrhoea than diphenoxylate and where patients who received loperamide had significantly better control of diarrhoea.
- Agreed that there was good evidence of the efficacy of loperamide, giving reassurance that there was little reason for the NDPSC's concerns regarding a potential lack of efficacy of one day's supply leading to continued use to achieve the desired therapeutic effect.
- Noted a guideline supporting the use of loperamide by travellers and for self-medication in adults with acute diarrhoea.
- Noted the application's assertion that the 2008 World Gastroenterology Organisation acute diarrhoea practice guidelines included children as young as 8 years in its recommendation of loperamide as the agent of choice for nonspecific antidiarrhoeal treatment in adults. Requested further details on the guideline.
- In relation to oral hydration, agreed with submitted data stating that the use of an oral hydration therapy compared to fluids taken when perceived as required, was of little (or no) additional value to travellers taking loperamide for relief of diarrhoea.

- Noted the recommended maximum dose of loperamide of 16 mg daily, representing the proposed maximum unscheduled quantity. Noted the applicant's statement regarding a wide therapeutic index with isolated reports of 144 mg and '60 doses' being consumed without fatal consequence. Noted that the fatal outcomes associated with loperamide overdose in the Periodic Safety Update Reports (PSUR XXXXX) were associated with multiple drug toxicity where the role of loperamide in causality was not defined.
- Noted that the application stated that loperamide was licensed for children over 2 years of age in the USA and Canada, and for children over 6 years or age in the UK (in a liquid format not yet available in Australia). It asserted that in the case of accidental ingestion, loperamide was demonstrated as not unsafe in children over 2 years of age.
- Noted NSW Poisons Information Centre (PIC) 2008 data which included 46 reports of loperamide poisoning, but no reported outcomes. Stated that the information from the NSW and Victorian PICs was largely limited to the proportion of all calls in which loperamide was involved. For both centres, the number was very small. In NSW, only 7 of 44 calls involving loperamide related to use in adults.
- The application stated that the risk of misdiagnosis of acute diarrhoea was very low as the symptoms of diarrhoea (stool consistency and stool frequency) were non-ambiguous and could be readily identified by the patient. It stated that a healthcare professional would usually rely on the patient's description of symptoms and would not initiate further diagnostic tests unless warning signs were present. The evaluator agreed that provided use was limited to no more than the contents of one packet in twenty-four hours, reinforced by labelling advice to seek medical advice if the diarrhoea persisted, the chances of inappropriately treating a misdiagnosed or masked serious illness were negligible.

(c) Toxicity and safety

- The application stated that the toxicity and safety of loperamide had previously been considered by the NDPSC as acceptable for OTC use. An additional 12 years of OTC Schedule 2 use was cited as evidence that loperamide had a favourable toxicity and safety profile.
- Noted previously submitted data of reported adverse events (AEs) associated with loperamide use in studies of patients with acute or chronic diarrhoea, assessed by the previous evaluator. Also noted the previously submitted table of post-marketing rates for AEs, agreeing that although the post-marketing AE rates were rare, under reporting was likely.
- Noted the previously submitted PSURs covering XXXXX. Stated that two important elements of a PSUR were statements as to whether:
  - an action had been taken by a regulator or the sponsor for safety reasons. Noted that in the XXXXX period, no such actions had been taken.

- the Reference Safety Information (the Company's Core Data Sheet-a corporate document which forms the basis for national product information) had been changed for a safety reason. In the period covered, there was one instance where changes were made to the "Undesirable effects" section (one each for loperamide, loperamide oxide and loperamide with simethicone [simethicone is an antiflatulent, currently unscheduled.]). This was the addition of 2 post-marketing adverse drug reactions: loss of consciousness and depressed level of consciousness.

· Asserted that this evidence suggested that the understanding of the adverse effects of loperamide as reflected in the product information was comprehensive and stable.

· Noted that AEs related to consciousness disturbance associated with loperamide (including loperamide+simethicone) occur primarily in children. Agreed that based on the estimated exposure for loperamide or loperamide with simethicone, the estimated reporting rates for these events were very rare.

· Noted records for 33 Australian reports of suspected AEs to loperamide-containing products from XXXXX, with no fatalities mentioned. Reports related to adults between 18 - 84 years with one report of a 3 year old child and two others where the age was not recorded. Twenty two reports implicated a loperamide-containing product as the sole suspected cause. There were 34 adverse reaction terms mentioned in those 22 reports. Of these adverse reaction terms, only three were mentioned more than once – nausea; chest pain and urticaria.

· Stated that although it was possible that the episodes of chest pain were not cardiac in origin, suggested that the sponsor consider updating the Australian Product Information (PI), specifically noting reports of chest pain from international sources.

· Stated that overall, there had been remarkably few reports to the TGA's Australian Registry maintained for reports of AEs.

· Noted a corporate report focusing on the reporting of adverse reactions to loperamide following OTC use. Stated that the report inaccurately equated OTC with non-prescription use and the analysis did not take into account that in some countries (e.g. Australia) OTC use may involve some degree of professional advice.

· Noted interactions of loperamide with other drugs in context of the approved PI and CMI. Stated that the CMI dated March 2009 contained non-specific and unhelpful information about interactions. Suggested that there was a need for the sponsor to update interaction information, so as to be more specific about which medicines had been shown, or on theoretical grounds were likely, to interact with loperamide and to identify those interactions, if any, that were likely to be clinically significant.

· Noted conditions in which loperamide use was contraindicated. Stated that provided the labelling stressed limiting use to the contents of one packet, and that the product was not to be used in the presence of high fever, blood in the bowel movements or on-going illness affecting the bowel, the contraindications could be effectively met.

Asserted that use in children under the age of 12 years must be expressly prohibited in the labelling.

- Noted that loperamide was a pregnancy category B3 drug and its use in pregnancy or breastfeeding was contraindicated. Stated that neither an attributable risk nor a conclusion of safety of loperamide in pregnancy was able to be conclusively determined from available evidence. Stated that in absolute terms any risk in pregnancy attributable to loperamide may be small, however agreed that the use of an icon to assist the communication of the contraindication information to individuals with low literacy would be beneficial.

(d) Dosage, formulation, labelling

Dosage

- For acute diarrhoea the recommended initial dose of loperamide in adults was 4 mg followed by 2 mg after each unformed stool. Daily dose should not exceed 16 mg.
- For chronic diarrhoea and reduction in volume of discharge of intestinal resections the recommended initial dose was 4 mg followed by 2 mg after each unformed stool until diarrhoea was controlled, after which dosage of loperamide should be reduced to meet individual requirements. When the optimal maintenance daily dosage has been established, this amount could then be administered as a single dose or in divided doses. The average daily maintenance dosage in clinical trials was 4 - 8 mg. A dosage of 10 mg was rarely exceeded. A temporary exacerbation of diarrhoea was controlled by increasing the loperamide dosage to achieve further control followed by titration back to the established maintenance dose.

Labelling

- The application listed the current warnings on the pack:
  - *"Should you have a fever or notice blood in your stools consult your healthcare professional";*
  - *"Do not use in pregnancy or lactation";*
  - *"Do not give to children under 12 years of age";*
  - *"If diarrhoea persists beyond 48 hours see your doctor".*
- The application also suggested additional warnings which could be considered based on previous NDPSC and MCC recommendations:
  - *"Seek medical advice if you suffer severe stomach pain".*
  - Guidance on hydration and recognising dehydration.
  - Guidance on spacing of dosing to avoid dose dumping by consumers taking multiple dosing in quick succession.
- Noted the application's aim to use patient-centred icons along with clear, concise instructions and/or precautions to improve comprehension among patients with low

literacy skills. Noted the application's suggestion that should the Committee feel that a greater emphasis should be placed on the pregnancy warning, the applicant would consider adding an icon cautioning sufferers against use in pregnancy.

- Noted, however that the current submission did not include a draft pack label and instead stated that the labelling would be assessed by the TGA and would meet all requirements in the Therapeutic Goods Order 69 and the *Required Advisory Statements for Medicine Labels*. Stated that in taking such an approach, the sponsor did not take advantage of an opportunity to demonstrate to the delegate/ACMS a solution to previous concerns regarding adequate labelling covering the long list of contraindications associated with loperamide and risk of inappropriate use as a result of the public's poor understanding of loperamide, its interactions and contraindications.

(e) Potential for abuse

- The application stated that reports of abuse or misuse associated with loperamide OTC were very rare, where most of the reported OTC cases were nonserious. Most cases reporting "intentional drug misuse" involved "incorrect administration duration" or "incorrect dose administered". Other reports involved overdose, maladministration, drug ineffective, and constipation. The only AE occurring with greatest frequency (3) was constipation, a labelled event.
- The evaluator noted expert comments that loperamide had been assessed to have a very low abuse potential, including a lack of evidence where loperamide could be used to achieve any CNS euphoric effect. Also noted expert comments stating that small pack size and cost were mitigators of inappropriate use or abuse.

(f) Any other matters to protect public health

- Noted that loperamide was available in 137 countries, mostly as an OTC product. Agreed that there was evidence of considerable safe use of loperamide as an OTC product in the USA, Canada and UK.
- Noted however that the applicant indicated that OTC in those countries equated with availability "in the grocery setting", and not some form of restriction to pharmacy outlets. Noted that the maximum doses in twenty-four hours were lower in the UK (6 x 2 mg) and USA (4 x 2 mg) compared to Australia. Asserted that data from clinical studies suggested that few consumers would need to take eight tablets in 24 hours.

Applicant's Response to the Evaluation Report

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

- Reiterated that the presentation of the packaging and labelling lay with the TGA and would be addressed separately from scheduling. Asserted that the main concerns which led to the NDPSC rejection in June 2010 were addressed in the application and stated that the ACMS was now in a position to determine the relevant required

warning statements believed to be key to a decision to exempt loperamide from scheduling.

- In response to the comment regarding greater specificity in loperamide interactions and differences between short-term and chronic use, noted that an error in the application could have contributed to the evaluator being misled into believing that interactions with chronic diarrhoea were also relevant for this proposal. Clarified that the proposal related to treatment of acute non-specific diarrhoea and acute non-specific chronic diarrhoea (acute episodes in patients who suffer from chronic conditions predisposing them to diarrhoea), not for chronic diarrhoea (i.e. long term use). Asserted that this was further supported by the loperamide Appendix F entry ("*Do not use beyond 48 hours*") for loperamide when included in Schedule 2.
- Clarified that the dose for both the Schedule 2 and proposed unscheduled presentations would be identical. Reiterated that the Expert Comment stated that clinically relevant drug interactions with short term use of loperamide had not been identified as a problem and that diarrhoea in Australia in the majority of cases was mild and short lived, indicating that chronic suffering was unlikely to occur.
- Supported the evaluator's recommendation that the labelling suggested in the Expert Comment be adopted for the exempt pack. Also noted the NZ MCC labelling recommendations for its exempt presentations of loperamide. Stated that Medsafe agreed that a pack insert would only be required if the labelling could not effectively cover advice on how to use the medicine safely. Proposed that Australian labelling should also include wording reflecting the NZ warnings. Provided a table of current and proposed loperamide warning statements.
- Asserted that as loperamide was listed as a Pregnancy Category B3 drug, the label already contained a precaution to seek healthcare advice if pregnant or breastfeeding.
- In response to the evaluator's proposal to review the AEs listed in the PI, noted that Schedule 2 products were not required to have an approved PI and one has only been maintained for historical reasons. Stated that this was updated accordingly based on the information in the company core data sheet.
- In response to a suggested shorter version of a CMI, asserted that as a pack insert was an extension of the product label, it was usually only included when all relevant product information could not be adequately communicated on the primary packaging. Asserted that this was reviewed on a case by case basis by the TGA to ensure acceptable presentation of the product.

June 2011 Pre-meeting Submissions

Four pre-meeting submissions were received. XXXXX, did not support the proposed exemption for loperamide. XXXXX, (gastroenterologists) supported the proposed exemption. The main points of these submissions have been summarised below:

XXXXX

Noted that the same proposal had previously been rejected by the NDPSC in June 2009 and June 2010.

Noted that Quality Use of Medicines (QUM) was one of the central objectives of Australia's National Medicines Policy and asserted that QUM was best supported by the supply of medicines through a pharmacy with access to specialised professional support and advice from a pharmacist. Hence they have traditionally opposed exempting medicines from scheduling stating concerns that the proposed arrangements may facilitate use of medicines in a manner that does not align with QUM principles.

Stated that there were no controls or quality assurance processes in place for supply of medicines through the grocery channel and customers with chronic conditions could purchase multiple small packs without any questions asked about the condition, patient history or medicine use. Asserted that access through the pharmacy sector was more than adequate and provided access to health professional advice to support QUM objectives.

The inclusion of warnings and directions on packs did not surmount the issues associated with poor consumer health literacy without the opportunity for counselling.

The submission also made a number of points specifically addressing criteria under section 52E of the Act, as summarised below:

(a) Risks and benefits

- Asserted that it was essential that the safety of vulnerable populations was protected when determining if a substance was to be exempt (including children, the elderly, those with co-morbidities or taking multiple medicines for chronic conditions and those whose first language was not English). Asserted that loperamide's safety profile was better aligned with a Schedule 2 listing, stating it was the least restrictive medicine classification which facilitated access to health professional support and advice.
- Noted an Italian epidemiological study on the prevalence of diarrhoea in old age, where the most common causes were infectious diseases (19 per cent) and drug use (16 per cent). Asserted the importance of rehydration and nutritional support in treatment of elderly patients with diarrhoea, regardless of cause. Asserted that for these types of situations, it was essential that patients had access to health professional advice.
- Stated that loperamide could cause tiredness, dizziness or drowsiness and noted its potential impacts on driving ability. Asserted that these effects were more noticeable with acute, short-term treatments (such as the proposed exemption) because the body was not yet accustomed to the effects of loperamide. Asserted that there was a potential interaction of loperamide with tranquilisers or alcohol which may also impact on driving ability.

(b) Purpose and extent of use

- Stool is 60 - 90 per cent water. Stated that in Western society, stool amount ranged from 100 - 200 g/day in healthy adults and 10 g/kg in infants (depending on the amount of unabsorbable dietary material). Diarrhoea is defined as stool weight of greater than 200 g/day. Stated that many people consider any increase in stool fluidity to be diarrhoea. Asserted that this demonstrated that the symptoms of diarrhoea could be ambiguous and self diagnosis was not necessarily a simple matter.
- Argued that the primary goal of treating diarrhoea, whether viral, bacterial, parasitic or non-infectious, was preventing dehydration or to provide appropriate rehydration. Asserted that most cases of acute diarrhoea were self limiting and did not require drug treatment.
- Asserted that if diarrhoea was prolonged or there was associated vomiting, blood in the stool, fever, or signs of dehydration, medical consultation was advised. Asserted that loperamide use should only be considered in adult patients who were not febrile or experiencing bloody/mucoid diarrhoea.
- Stated that antidiarrhoeals should not be used for acute diarrhoea in children as they do not reduce fluid and electrolyte loss, may delay expulsion of organisms and/or cause adverse effects.
- Stated that the dehydrating effect of diarrhoea was often underestimated, especially in a hot climate. Stated that dehydration may be less noticed in the elderly who often fail to experience appropriate thirst.
- Noted possible complications resulting from diarrhoea, including fluid loss, electrolyte loss and vascular collapse (in patients with severe diarrhoea or patients who are very young, very old or debilitated).
- Stated that in chronic diarrhoea, it was important to consider other causes such as coeliac disease and inflammatory bowel disease and the need for further assessment if alarm symptoms were noticed.
- Noted an article in the Medical Journal of Australia stating that Australia was in the grip of a new strain of *Clostridium difficile*, the most common infectious cause of nosocomial diarrhoea for which the severity of infection could vary from mild diarrhoea to pseudomembranous colitis, toxic megacolon and death. Stated that the article advised that Australia should learn from overseas experiences and implement necessary interventions. Stated that pharmacists were well placed to assess whether patients with mild diarrhoea had any recent hospitalisation to facilitate referral for further investigation.
- Noted that loperamide was commonly included as part of a traveller's first aid kit, particularly when travelling overseas. Stated that the traveller would benefit from interaction with pharmacy personnel who could also assist with other travelling contingencies.

- Stated that with exempt preparations there was no quality assurance processes to restrict the number of packs purchased or monitor purchase frequency.
- Asserted that there were significant risks attached with misdiagnosis or misuse of loperamide and mild diarrhoea can develop into a life-threatening condition, depending on its cause.

(c) Toxicity

- Listed loperamide's contraindications and where it should be used with caution. Noted loperamide's pregnancy category (B3) and stated it was not recommended in either pregnancy or lactation.
- Stated that due to these safety concerns, even short-term treatment of acute diarrhoea would be better managed through a pharmacy with access to professional advice.

(d) Dosage, formulation, labelling

- Noted common assertions in exemption applications that risks could be mitigated through labelling. Raised concerns that people may not read labels, and when they did often may not understand the content.
- Referred to an Australian Bureau of Statistics survey indicating that a number of Australians (including people whose language was not English) did not have sufficient literacy skills to meet the complex demands of everyday work and life, and that on the health scale, 60 per cent attained scores below the minimum requirement to meet everyday needs. Stated that in the interest of public safety, it was essential to aim support at people with limited health literacy.
- Raised concerns that even small packs may be inadvertently misused. Stated that while retaining loperamide in Schedule 2 may not resolve this issue in every instance, it would ameliorate it and provide consumers with the opportunity to receive informed advice if required.

(e) Potential for abuse

- Stated that although it had the lowest addiction potential of all opioids, loperamide may cause sedation, nausea and cramps. Stated that there was more risk of inappropriate use than abuse associated with unrestricted access to loperamide.

(f) Other matters

- Asserted that access to Schedule 2 loperamide was appropriate noting the wide distribution of pharmacies and increases in extended trading hours. Noted that country pharmacists also provided after-hours patient access for urgent cases. Stated that it was common for pharmacies in both rural and metropolitan areas to offer delivery services for local areas.
- Stated that in some jurisdictions, store trading hour regulations meant that after-hours pharmacy access may be as good as or better than that through the grocery sector.

- Stated that from 1 July 2009 pharmacists were allowed to issue certificates as proof of legitimate absence from work. The Pharmacy Guild of Australia developed a reference guide with input from clinical stakeholders with recommendations for the issue of a 24 hour certificate for patients with diarrhoea and when to refer the patient to a doctor.

XXXXX

- Reiterated points from the June 2010 NDPSC discussion. Noted that its submission to that consideration also opposed a loperamide exemption.
- Reiterated the above-mentioned point that diarrhoea could be life-threatening if not managed appropriately. Reiterated above-mentioned points regarding the need for timely access to loperamide from an environment where pharmacist intervention would be available.

XXXXX ***(gastroenterologist)***

- Stated that loperamide should be more readily available for patient use as it was a common medication in traveller's medication kits and was used frequently and safely in this setting in the absence of medical/pharmacist advice. Asserted that there was no reason it could not be used similarly in the community.
- Asserted that as loperamide was already available in a general sales environment through the internet the restriction of the location of physical sales was less relevant.

XXXXX ***(gastroenterologist)***

- Asserted that a one day or maximum eight tablet supply would allow excellent symptom control for patients with acute infectious (viral or bacterial) gastroenteritis and would not be detrimental to the course of the illness or cause delay in diagnosis.
- Stated that patients could be advised to see their GP if symptoms persisted beyond this time or if they had more worrying features such as rectal bleeding. Stated that these caveats could be included on the packaging.

New Zealand April 2010 MCC minutes

In April 2010, the MCC agreed that loperamide should be reclassified from pharmacy-only medicine to general sale medicine in divided solid dosage forms for oral use containing 2 mg or less of loperamide when sold in a pack containing not more than eight approved by the Minister or the Director-General for distribution as a general sale medicine, for the symptomatic treatment of acute non specific diarrhoea.

The MCC recommended that the label include guidance on seeking advice from a healthcare practitioner. The MCC also recommended that the product information to be inserted into the pack should include advice on:

- checking with an employer if diarrhoea may put others in the workplace at risk

- hand washing and hygiene
- hydration (in addition to what is already provided)
- recognising dehydration.

The minutes from the meeting also noted:

- Although diarrhoea was a common ailment it could escalate to a potentially serious condition if not managed appropriately.
- The safety of the product was derived to some extent from the proposed limited pack size of eight caplets or capsules. However, there was no control to prevent patients purchasing large amounts through multiple packs whereas requests for multiple packs would be questioned in a pharmacy.
- Raised concern that retail sale could lead to inappropriate long-term use of loperamide. However, it was noted the PSURs submitted showed loperamide was widely available and used overseas at the general sale level. Also that its use was not associated with reports of significant harm.
- The MCC raised concern that reclassification of loperamide could lead to inappropriate use of the product in occupations where individuals with a diarrhoeal illness should be temporarily excluded e.g. food handling. However, it was considered that this issue could be addressed by inclusion of general advice about hydration and hygiene if suffering from diarrhoea.
- The MCC concluded that with appropriate labelling the safety profile of loperamide supported its reclassification to general sale medicine for the symptomatic treatment of acute non-specific diarrhoea.

June 2010 NDPSC Discussion

Members noted the NDPSC loperamide discussion at the June 2010 meeting:

- The NDPSC generally agreed that the prevention of dehydration was the first line of treatment for diarrhoea. An NDPSC Member asserted that a focus on consumer management of dehydration was especially important due to Australia's arid environment, where associated risks were greater than in other countries (i.e. Canada or the UK).
- NDPSC Members noted the long list of contraindications associated with loperamide and raised concerns that CMI was not required for unscheduled products. A Member asserted that although CMIs were not mandatory, this would not necessarily indicate a deficiency in the unscheduled products' label warnings. The Member argued that the regulator would ensure that labelling and warning statements were appropriate.
- Another NDPSC Member asserted that the public had a poor understanding of loperamide and its interactions and contraindications. The Member further argued

that as a large percentage of the population did not read packet instructions there was a risk that loperamide may be used inappropriately.

- An NDPSC Member argued that a limited exemption for only one days' supply would minimise the potential risks. Another Member argued that there were questions as to the efficacy of one day's supply and in the absence of a desired effect consumers may continue to use loperamide, through purchase of multiple packs, without obtaining appropriate advice or information if such was not readily available. Another Member noted that there had already been reports of the misuse of loperamide, which may be indicative of a wider problem. The Member asserted that there was a risk that this misuse may be exacerbated if loperamide was to be available as unscheduled.
- The NDPSC noted the claim that an exemption for loperamide would ensure access in rural areas. Several NDPSC Members noted that there exist alternative supply provisions which ensure appropriate access to scheduled substances, especially in rural areas where pharmacies may be limited or difficult to access.
- The NDPSC acknowledged that consumers experience a degree of urgency when seeking access to loperamide. However, a Member asserted that it was important for consumers to be able to obtain advice and information for loperamide and that scheduling would ensure that this was available. The NDPSC generally agreed that, on balance, it was not appropriate for loperamide to be available as unscheduled.

EXPERT ADVISORY COMMITTEE DISCUSSION

XXXXX.

A Member reiterated that loperamide was not a first line treatment and argued that decreasing scheduling restrictions may inadvertently send such a message. Other Members noted that while hydration was the first line treatment, there were benefits in the concurrent use of loperamide for symptom control.

A Member also raised concerns regarding the contraindications for loperamide, its interactions with quinidine and its lack of efficacy in the treatment of other causes of diarrhoea. A Member also drew the Committee's attention to animal studies which show mild opiate withdrawal on discontinuation of loperamide. However, other Members generally agreed that loperamide was considered safe and efficacious when used appropriately.

The Committee noted the comments supporting loperamide exemption from expert gastroenterologists which were provided by the applicant. A Member asserted that these comments made assertions on the psychology of consumer behaviour which would not necessarily be an area of expertise for gastroenterologists. However, another Member disagreed and argued that such experts' professional opinions should be given weight due to their experience in the use of loperamide and the treatment of patients presenting with gastric symptoms.

A Member stated that loperamide products were available on the internet, which was broadly equivalent to being available as general sale. Other Members disagreed and noted that certain restrictions still applied through online pharmacies which were not present for general sale. However, Members generally agreed that internet supply was not necessarily relevant to the current consideration as consumers seeking to urgently relieve an acute episode of diarrhoea would not be seeking to use such a slow supply avenue.

Members discussed the current use patterns of loperamide products and the risks of misuse if an exemption from scheduling was allowed. A Member asserted that loperamide was used for symptom control, not treatment of underlying condition. The Member stated that as these symptoms were self-limiting, the risks of long-term use of loperamide were low. The Member also stated that small packs and the use of labelling would also help to ensure appropriate use of loperamide. A Member raised concerns that in certain countries loperamide was inappropriately marketed for use in children. However, another Member noted that this matter had since been largely resolved overseas and in Australia such loperamide products were restricted to treatment of adults and children over 12. Members generally agreed that, on-balance, the overall benefit of access to small packs of loperamide as exempt from scheduling outweighed the potential risks. Members also noted that such an exemption would essentially harmonise with the NZ scheduling of loperamide.

Members discussed whether the exemption should apply to all dose forms of loperamide. Specifically, a Member queried whether that the exemption should exclude fast dissolving and chewable tablets due to their risk of accidental ingestion by children. However another Member clarified that these dose forms of loperamide did not present a higher toxicity concern compared to the tablet form. A Member also stated that there could be additional benefits in allowing fast-dissolving tablets to be exempt due to improved absorption. Members generally agreed that the product approval process was better suited to determine the suitability of different dose forms.

Members also agreed that appropriate labelling would be required to ensure safe use of loperamide products. Members agreed that to help inform the TGA's consideration of these labelling requirements, the expert opinions on the labelling of loperamide products should be provided to the relevant TGA registration area.

Implementation date

Members discussed appropriate implementation timeframes for this decision. Members agreed on an implementation period of at least 6 months to allow time for companies to manage existing stock.

Other matter – Appendix F

Members also considered whether an Appendix F entry for loperamide preparations captured by Schedule 2 was still required. Member noted that labelling requirements for OTC medicines were regulated through the TGA's RASML.

RASML included a requirement for loperamide when included in Schedule 2 to be labelled with statements 6 (*Do not give to children under 12 years of age*) and 17 (*Do not use beyond 48 hours or in pregnancy or lactation except on doctor's advice*). These requirements were consistent with the SUSMP Appendix F entry for loperamide when in Schedule 2. The only application of the Appendix F labelling would therefore be where a loperamide preparation was not regulated by the TGA (i.e. dispensed as a compounded preparation).

Members noted that while Appendix L was intended to have replaced Appendix F for setting out minimum labelling requirements for medicines not subject to RASML (i.e. dispensed as a compounded preparation), not all jurisdictions had as yet made this transition in their own legislation. Members agreed that as some jurisdictions still referenced the Appendix F entries it was not yet appropriate to delete human therapeutic substances, such as loperamide, from this appendix.

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, labelling, packaging and presentation of the substance.

DELEGATE'S INTERIM DECISION

The delegate decided to exempt loperamide in divided preparations for oral use containing not more than 2 mg of loperamide in packs of 8 dosage units or less. The delegate decided on an implementation date of 1 May 2012.

The delegate also agreed to communicate the evaluator's labelling recommendations to the appropriate area within the TGA.

SUBMISSIONS ON INTERIM DECISION

One further submission was received from XXXXX opposing the interim decision and recommending that a minimum Schedule 2 listing for loperamide should be retained.

The submission also made several points, as summarised below:

XXXXX

- Reasserted that there was no identified need to exempt loperamide from scheduling. Stated that it had not been shown that the Australian public was disadvantaged by loperamide being a Schedule 2 medicine. Reiterated points regarding pharmacy and grocery outlet trading hours.
- In relation to the application's comment that "withholding treatment of symptoms with loperamide in the absence of warning signs would be unnecessary and would exacerbate the distress of the disorder", clarified that access was being denied or delayed from the pharmacy sector. Asserted that a study showed that the most common reason for non-purchase of a Schedule 2 medicine did not relate to access but to the consumer not wanting to use medicines or treatments, or not believing medicines were required.
- Asserted that international regulatory status should not be used as a precedent for scheduling decisions. Stated that other countries do not have as effective a scheduling system as Australia, with usually either one or nil OTC categories. Asserted that in relation to harmonisation with NZ, the NZ decision was based on matters of relevance to NZ which may not be appropriate for Australia. Suggested that if harmonisation was an issue, NZ should instead harmonise with Australia's Schedule 2 loperamide status.
- Raised concerns that travellers who purchase loperamide for later use may rely solely on this product as the diarrhoea treatment. Noted a European study which indicated that a proportion of Europeans feel that it is sufficient to include loperamide alone in the travel kit for routine treatment of travellers' diarrhoea. Asserted it was important for travellers to also have antimicrobial therapy available for treatment when dysentery (passage of blood stools) or high fever may be a complication, particularly if going to remote areas in countries with limited access to quality-assured prescription medicines. Noted that antisecretory agents (such as loperamide) were not advised where there was fever or bloody diarrhoea and instead, an antibiotic should be used with extra fluids as first line therapy.
- Asserted that it was inappropriate that mitigation of safety issues relied significantly on effective labelling and packaging. Raised concerns that a significant amount of cautionary labelling was required to address safety concerns. Raised concerns regarding the type of packaging and labelling which may be utilised. Detailed concerns regarding consumer's ability to read and understand medicine labels. Reiterated previously noted health literacy statistics.
- Noted that UK conditions for general sale of loperamide required a package insert which detailed when medical advice should be sought. Asserted it was unlikely that a patient would read this insert when feeling unwell.
- Asserted that the arguments of three gastroenterologists included in the application did not demonstrate a public benefit for exempting loperamide from scheduling and the comments related more to the efficacy of the scheduling system rather than the scheduling of loperamide. Asserted that a comparison with the safety profiles of

other unscheduled substances should not be used as a precedent for scheduling. Raised concerns regarding the value of these opinions and queried whether the Gastroenterological Society of Australia supported the proposed rescheduling.

- Stated that the availability of medicines over the internet was problematic. Stated that there were professional guidelines and standards for the supply of Schedule 2 medicines from Australian pharmacies, managed through the Pharmacy Board of Australia. Asserted that internet sales should not be seen as a precedent for unrestricted supply.
- Reiterated that access to professional advice on loperamide use should be facilitated, particularly for more vulnerable population groups. Reiterated that the grocery sector lacked quality assurance processes for provision of medicines. Noted the extent of training undertaken by pharmacy assistants and assessments of pharmacy performance when supplying OTC medicines.

DELEGATE'S RECONSIDERATION OF INTERIM DECISION

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

The delegate again noted ACMS Members' discussion of the risks and benefits of loperamide when exempt from scheduling and agreed that, on-balance, the overall benefit of access to small packs of loperamide as exempt from scheduling outweighed the potential risks.

The delegate agreed that the interim decision was appropriate and that small packs of loperamide for oral use (up to 8 dosage units) containing not more than 2 mg of loperamide per dosage unit should be exempt from scheduling.

DELEGATE'S FINAL DECISION

The delegate decided to exempt loperamide in divided preparations for oral use containing not more than 2 mg of loperamide in packs of 8 dosage units or less. The delegate decided on an implementation date of 1 May 2012.

The delegate also agreed to communicate the evaluator's labelling recommendations to the appropriate area within the TGA.

Schedule 2 – Amendment

LOPERAMIDE – Amendment to read:

LOPERAMIDE in divided preparations for oral use in packs of 20 dosage units or less **except** in preparations containing 2 mg or less of loperamide per dosage unit, in a primary pack containing 8 dosage units or less.

Schedule 4 – Amendment

LOPERAMIDE – Amendment to read:

LOPERAMIDE **except:**

(a) when included in Schedule 2; or

(b) in divided oral preparations containing 2 mg or less of loperamide per dosage unit, in a primary pack containing 8 dosage units or less.

2.1.2 NICOTINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Nicotine – proposal to amend the Schedule 4 entry to exempt from scheduling, when used for human therapeutic use as an aid in withdrawal from tobacco smoking:

· nicotine oromucosal film; and

· nicotine inhalation cartridges for oromucosal use.

These proposed exemptions are similar to the exemptions for nicotine in chewing gums, lozenges, and preparations for sublingual, transdermal or oromucosal spray use when used as an aid in withdrawal from tobacco smoking.

ACMS advice is also sought on potentially expanding the nicotine exemption to include all oromucosal uses.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the Schedule 4 exemption for nicotine in preparations for human therapeutic use be extended to include all oromucosal use (i.e. essentially harmonised with New Zealand scheduling for nicotine for human therapeutic use). The Committee also recommended the inclusion of a definition of 'oromucosal' in SUSMP Part 1, Interpretation.

The Committee also recommended deletion of the Schedule 2 nicotine entry (i.e. all nicotine inhalation cartridge preparations for oromucosal use as aids in withdrawal from tobacco smoking would become exempt with any other inhalation preparations for human therapeutic use being captured by Schedule 4).

The Committee recommended an implementation date of no more than 6 months after the delegate's final decision (i.e. 1 January 2012).

BACKGROUND

The first-line pharmacological intervention for nicotine dependence from cigarette smoking is nicotine replacement therapy (NRT). NRT formats currently available over-the-counter (OTC) include chewing gum, lozenge and inhaler (absorbed via the buccal mucosa), patch (transdermal) and microtab (sublingual). Combination therapy with different types of NRT has also been tried as a means of increasing efficacy.

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

In August 1993, the NDPSC rejected a proposal to have 2 mg sublingual tablets rescheduled from Schedule 3 to Schedule 2 and 4 mg sublingual tablets rescheduled from Schedule 4 to Schedule 3. In November 1993, the NDPSC agreed that Schedule 4 remained appropriate for patch formulations. Subsequently, in November 1997, transdermal patches were included in Schedule 3.

Nicotine 2 mg chewing tablets were rescheduled to Schedule 2 in February 1997. However, at the same meeting the NDPSC decided that the higher dosage (4 mg) should only be rescheduled to Schedule 3 to facilitate the counselling of heavy smokers by a pharmacist.

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

In November 1998, the NDPSC considered downscheduling nicotine for inhalation, when packed in cartridges for use as an aid in withdrawal from tobacco smoking, from Schedule 4 to Schedule 3 and decided that Schedule 3 was appropriate. The NDPSC noted that this form of oral inhalation was similar in many respects to the chewing gum, being absorbed mainly in the mouth and throat. Data provided indicated that nicotine plasma levels obtained via the inhaler were similar to those obtained with the 2 mg chewing gum.

In February 1999, the NDPSC amended this Schedule 3 nicotine entry to 'Nicotine as an aid in withdrawal from tobacco smoking in preparations for inhalation or sublingual use'.

In August 2001, the NDPSC agreed that nicotine lozenges would have a comparable safety profile to that of sublingual tablets, and so it was appropriate to also include lozenges in Schedule 3. Subsequently, lozenge preparations were down scheduled to Schedule 2 in June 2003. In February 2002, nicotine inhalers were rescheduled from Schedule 3 to Schedule 2.

In February 2010, the NDPSC considered an application to broaden the exemptions for specified NRT buccal dosage formats i.e. chewing gum and lozenges, to buccal

preparations in general. The NDPSC decided to only down-schedule oromucosal sprays and did not support an exemption for oromucosal preparations in general, noting that this could potentially include preparations such as mouthwashes. The NDPSC was of the opinion that there was insufficient data for such a broad exemption.

In June 2010, the NDPSC noted a post-meeting submission requesting that the exemption either be reworded to all oral use or all oromucosal products which were bioequivalent to currently marketed oral dose formats. This request was not supported and the NDPSC confirmed its February 2010 decision.

The current consideration was a result of referral of two separate requests to exempt nicotine in two different presentations. As part of a TGA registration application, XXXXX requested exemption from scheduling of oromucosal dissolving buccal film strips containing XXXXX nicotine. XXXXX also submitted an application direct to the Scheduling Secretariat seeking an exemption for nicotine oromucosal preparations in general or a specific reference to "inhalation cartridges for oromucosal use". The delegates agreed that these were matters warranting advice from the ACMS and referred them to the June 2011 ACMS meeting.

SCHEDULING STATUS

Nicotine for human therapeutic use when in preparations for inhalation for use as an aid in smoking cessation is captured by Schedule 2. Chewing gums, lozenges, or preparations for sublingual, transdermal or oromucosal spray use containing nicotine when for human therapeutic use as aids in smoking cessation are exempt from scheduling. All other preparations of nicotine for human therapeutic use are captured by Schedule 4.

Preparations of nicotine other than for human therapeutic use are either captured by Schedule 6, Schedule 7 or exempt depending on the use pattern.

INITIAL SUBMISSIONS

XXXXX ***via TGA – buccal film***

The TGA referred a request from XXXXX for exemption from scheduling of an oromucosal dissolving buccal film containing XXXXX nicotine for use as NRT, to aid in withdrawal from tobacco smoking. The TGA supported the proposed exemption for the oromucosal film and noted the following points, summarised below:

- Noted nicotine replacement therapy dosage forms either registered on the ARTG for use in Australia, or currently being evaluated by the TGA:

Chewing gums	Unscheduled
Transdermal patches	Unscheduled
Sublingual tablets	Unscheduled

Inhalers	Schedule 2
Lozenges	Unscheduled
XXXXX	XXXXX
XXXXX	XXXXX

TGA further information

XXXXX. The TGA also provided the following additional information to help inform the ACMS consideration:

- Nicotine containing oromocosal film was a new oral form of intermittent-dosing NRT. The term 'intermittent-dosing' NRT referred to products (such as nicotine chewing gums and lozenges) that were administered when needed to provide relief of nicotine withdrawal symptoms – rather than products such as transdermal patches which provided a constant dose of nicotine (eg. currently available for 16 or 24 hour release).
- The dose of nicotine is administered by placing an oromucosal film strip on the tongue then pressing the tongue onto the roof of the mouth. The film then dissolves in approximately 3 minutes, allowing buccal absorption of the nicotine.
- XXXXX
- Nicotine containing oromocosal film was approved for use in a number of European countries on 5 May 2011.

Efficacy & safety

- Although the strips presented a new delivery system for nicotine, the route of administration (buccal) was the same as for currently registered nicotine chewing gums, lozenges, sublingual tablets and inhalers.
- XXXXX
- The bioequivalence study compared nicotine strips with existing NRT treatments. XXXXX
- The bioequivalence study demonstrated that the nicotine XXXXX oral strips are bioequivalent to a currently Australian registered XXXXX lozenge (and to a comparator XXXXX gum), in terms of the C_{max} (maximum concentration of a drug in the body after dosing) and AUC (area under the curve).
- Although the oral strip dissolved in the mouth faster than the gum or lozenge, its T_{max} (time to reach C_{max}) was longer than that of either of the comparators. Intermittent dosing NRT forms were intended to be used regularly throughout the day (eg. every 1-2 hours), to establish a relatively constant blood nicotine concentration to help reduce nicotine withdrawal symptoms associated with quitting smoking.

- Based on the blood nicotine concentrations available within the first ten minutes of product administration, the onset of action in nicotine craving relief with the XXXXX oral strip would be the same as for the reference lozenge and gum. The evaluator concluded that additional data supporting the efficacy of the XXXXX oral strips were not required, XXXXX.
- In both the bioequivalence and tolerability studies, the adverse events seen with the oral strips were consistent with the known adverse event profile of nicotine using other forms of NRT for buccal absorption.

Wording of scheduling exemption for nicotine

The TGA requested that the order of presentations listed in the exemption clause in Schedule 4 be amended:

- from the current entry listing: "*chewing gum, lozenges, or preparations for sublingual, transdermal or oromucosal spray use*"
- to: "*chewing gum, lozenges, oromucosal film* (if agreed), *oromucosal spray, or preparations for sublingual or transdermal use*.".

XXXXX – ***inhalation cartridge***

XXXXX requested an exemption from scheduling for all oromucosal preparations in general. Alternatively, the applicant requested that the exemption be amended to include the specific dosage format "inhalation cartridge for oromucosal use".

Members noted that the application referred to material previously submitted as part of applications considered by the NDPSC in November 1998 and February 2002.

The application made a number of points, summarised below:

- The inhaler consists of a porous plug of polyethylene which contains nicotine (currently available in 10 mg or 15 mg) as the active and menthol as a flavour. The plug is packaged in a transparent tube which is sealed at both ends with aluminium foil. Prior to use the tube is inserted in a mouthpiece and the seals are broken. When air is drawn through the plug gaseous nicotine and menthol are released.
- A buccal route of absorption pertains to the check cavity whilst a sublingual route of absorption infers absorption beneath the tongue. Oromucosal preparations pertain to the oral mucosa i.e. the entire mouth, thus including both buccal and sublingual preparations.
- Asserted that the Schedule 2 nicotine entry for nicotine was for preparations for inhalation through the lungs, not for preparations with an oromucosal route of absorption. Claimed that due to the wording of the exemption, inhalation cartridges

were inappropriately captured by the Schedule 2 nicotine entry, implying the product was for inhalation.

- Asserted that as the inhalation cartridge had a buccal route of absorption (similar to oromucosal sprays) it should be exempt from scheduling. The drug product is drawn into the mouth (inspiration) rather than the lungs (inhalation). The major proportion of the dose is deposited in the oral cavity and absorbed oromucosally, with only a minor fraction of the nicotine reaching the lungs. Stated that less than 5 per cent of the nicotine absorbed after inhaler use reaches the lungs.
- Claimed that nicotine is highly soluble in water and due to the absence of carbon particles and droplets nicotine from the inhaler is unable to be carried to the lungs unlike nicotine delivered in cigarettes. Additionally, cigarette smoke is acidic (pH around 5.5), thus nicotine is ionized and little absorption occurs through the oral mucosa. Once the smoke from a cigarette reaches the small airways and alveoli it is buffered to a higher pH resulting in a greater absorption of the nicotine.
- Claimed that there was no need to separate buccal and sublingual formats as oromucosal preparations regardless of dosage format have comparable safety and efficacy profiles and grouping them together would be logical. Provided a table comparing the routes of absorption of nicotine from chewing gum, inhalers and sublingual tablets.
- Stated that continuous, rapid inhalation over 20 minutes (with a 10 mg inhaler) or 40 minutes (15 mg inhaler) would release up to 40 per cent of the nicotine from each cartridge, where about 50 per cent of the released nicotine would be systemically available, i.e. about 2 mg (10 mg inhaler) and 4 mg (10 mg inhaler). Absorption of nicotine through the buccal mucosa is slow and does not produce the high and rapid nicotine plasma concentrations seen with cigarette smoking. Self administration typically produced nicotine plasma concentrations of 8-10 ng/mL, which are approximately one third of those achieved with cigarette smoking. The plasma concentrations following clinical use corresponded to once hourly chewing of 2 mg chewing gum.
- Referred also to data submitted as part of the November 1998 NDPSC consideration stating that the inhaler had a similar route of absorption (buccal) and safety profile to nicotine chewing gum. Stated that the similarity of the inhaler to nicotine chewing gum provided support for a similar exemption from scheduling.
- Provided a graph depicting the delivery of nicotine from an inhaler which was similar to, or slower than other oral exempt NRT formats.
- Stated that there was an established principle that certain NRT products may safely be sold as general sale and did not require a pharmacist to supervise the sale. Stated that apart from toxicity, all available NRT presentations fulfilled the scheduling criteria under section 52E of the *Therapeutic Goods Act 1989* to a similar degree.
- Noted that new dosage formats were reviewed by the TGA and required supporting clinical studies. Asserted that, therefore, an exemption for oromucosal preparations

in general would not see the expansion to less suitable formats, as the TGA would assess the safety and efficacy of new dosage formats.

- Stated that the inhaler became available as OTC in Australia over 10 years ago and was available for self selection as a Schedule 2 product in this time period. In 2009, the inhaler was rescheduled from Pharmacy Only to General Sale in the United Kingdom, acknowledging that the product was an "inhalation cartridge for oromucosal use".
- Stated that the safety profile of inhalers was well characterised. Following over 10 years of marketing in Australia no new adverse drug reactions or risks associated with use of inhalers had been identified. Stated that drug interactions with nicotine were very rare and clinical significance was generally not established.
- Noted that benefits specific to this presentation included assisting people with dentures, a jaw condition or those that required support from hand-to-mouth smoking behaviour would then be assisted to quit who would otherwise fail.
- Asserted that the risk of the inhalation cartridge masking a serious disease or compromising medical management of a disease was similar to other NRT products.
- Asserted that cigarettes were a more likely option for abuse compared to inhalers due to their relative ease of access and ability to rapidly give pleasurable effect (effects which were not induced by the inhaler).

February 2002 NDPSC consideration

Members noted a number of relevant points from the discussion of nicotine inhalers at the February 2002 NDPSC meeting:

- The NDPSC agreed to include nicotine inhalers for use as an aid in withdrawal from tobacco smoking in Schedule 2. The NDPSC noted the evaluator's comments that:
  - The indication and proposed use of the nicotine inhaler was consistent with unscheduled products and unlikely to compromise medical management of other diseases.
  - The nicotine inhaler had a good safety and side-effect profile, consistent with other NRT products including the chewing gum, with the exception of the local effects of the inhaler (irritation in the mouth and throat, sinusitis, nasal congestion and aphthous ulcer).
  - The influence of inspired air temperature on bioavailability may impact the frequency of use of the inhaler, given that subjects determine their own dosing frequency, however, it would be unlikely that this would lead to any significant safety issues.
- The NDPSC supported the claim that the success rate in ceasing smoking had been associated with the level of exposure and access to NRT products. However, it was also stated that it was essential for support mechanisms including access to

counselling to be the same across all NRT products for a holistic approach to smoking cessation.

- The NDPSC noted that the initial concerns regarding the potential for the nicotine inhaler to sustain behavioural aspects of cigarette smoking was not supported by evidence in the post-marketing data provided by the applicant, possibly due to differences in absorption sites, i.e., oral mucosa vs the lung, and differences in the mode of action between cigarettes and the nicotine inhaler.

February 2010 NDPSC consideration

Members noted a number of relevant points from the discussion of nicotine inhalers at the February 2010 NDPSC meeting:

- The NDPSC considered an application to exempt to broaden the nicotine exemption to buccal preparations in general.
- The evaluation report recommended approval of an exemption for oromucosal spray products, pending supportive evidence of safety and efficacy. The evaluator argued that should such data be provided, and an exemption be considered for all buccal preparations, then for greater clarity, the following wording should be used "for use as an aid in withdrawal from tobacco smoking in preparations for oromucosal or transdermal absorption". However, the evaluator noted that the data in the application was not sufficient to support the proposal.
- The NDPSC noted that a general exemption for all buccal preparations would allow for new, innovative formats, such as, for example, oromucosal spray. A potential benefit in encouraging new options would particularly be for those few who were unable to chew, maintain a lozenge in the mouth or maintain a patch on the skin. Several Members, however, felt that such an exemption would be too broad and could potentially see it expand to less suitable formats such as mouthwashes and toothpastes.
- The NDPSC generally agreed that the only potential addition for exemption at this time, for which data had been presented, was a specific exemption for oromucosal spray formats.
- There was concern regarding the risks of ingestion by consumers, particularly children, of a dose of liquid containing nicotine from a spray format. Members noted, however, that both the systemic availability of nicotine and the concentration of nicotine in a spray would be low, which would reduce any risk of unwanted systemic effects.
- The NDPSC also confirmed that the exemption for oromucosal spray use was not intended to exempt the current Schedule 2 NRT inhalers.

November 2010 MCC consideration

In November 2010 the MCC recommended that the general sale classification of nicotine should be amended from 'for transdermal use in chewing gum, lozenges or sublingual

tablets' to 'for preparations for oromucosal or transdermal absorption'. This consideration included nicotine in mouth sprays and inhalation cartridges for oromucosal use.

Overall the MCC was comfortable with the submission and noted that the data presented showed that the different dose forms were similar even though bioequivalence data had not been included in the submission.

The MCC also noted that as the major portion of the dose from the nicotine inhaler was deposited in the oral cavity, so use of the term 'inhaler' was potentially misleading. The MCC preferred the use of the term "inhalator" to better describe the presentation.

June 2011 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX.

XXXXX did not object to an exemption from scheduling for oromucosal film and inhalation cartridges for oromucosal use, however did not provide further comment. XXXXX supported the proposal to exempt oromucosal film strips but did not comment on other oromucosal presentations. XXXXX supported the proposal to expand the exemption to include all oromucosal uses.

XXXXX supported standardising the scheduling category for all NRTs, however stated that these should be included in Schedule 2.

The submissions reiterated many points raised previously by the two applications. The main points not mentioned previously have been summarised below:

XXXXX ***(oromucosal film)***

- Stated that NRTs had a wide safety margin and extensive experience (over 20 years of use) demonstrating a favourable safety profile with few significant untoward effects, even in those with cardiovascular disease or who use NRT and smoke.
- Stated that nicotine in lozenges and gum was well-tolerated and exposure to nicotine with other oromucosal forms of nicotine was likely to be the same as with these presentations.
- Stated that smokers could identify nicotine (tobacco) withdrawal symptoms and cravings. Noted that current exempt forms of NRT did not require professional counselling before use. Asserted that as oromucosal strips would be used in much the same way as other exempt dose formats there would be no need for professional counselling before use.
- Stated that the potential for abuse for oromucosal strips would be similar to that of currently marketed oral dose formats, which was negligible.

- Stated that the risk of NRT masking a serious disease or compromising medical management of a disease was low and consistent with other exempt NRT presentations.

XXXXX

- Stated that since the start of NRT in 1988 (as chewing gum) a number of different dosage forms had become available and as each new form was evaluated, confidence was generated that the various routes of administration had similar profiles in relation to criteria under section 52E of the Act.
- Stated that due to the TGA's regulatory guidelines in the introduction of new dosage formats there was sufficient evidence to support exempting all oromucosal use from the Schedule 4 entry.
- Noted that neither the SUSMP nor the *TGA Approved Terminology for Medicines* define 'oromucosal'. Provided the definition of oromucosal from the European Pharmacopoeia as an example. Suggested that such a definition should be included in the SUSMP to avoid the unintentional removal of a dose form from the exemption (noting that some definitions of oromucosal may not clearly capture chewing gum).

XXXXX

- Stated that there was no evidence of significant difference in effectiveness between NRT patches, lozenges, gums, tablets or inhalers, with the main difference being the choice between transdermal application and oral absorption.
- Stated that NRT was more likely to be effective (and cost-effective) when therapy included both a product and concurrent professional support. Stated concerns that the exempted status of NRTs may undermine the desired outcome of quitting.
- Noted the Pharmaceutical Benefits Advisory Committee's (PBAC) March 2010 recommendation to list transdermal nicotine patches on the PBS which included conditions relating to attendance of support and counselling programs. Stated that this was further evidence of the importance of professional support in tandem with NRT products.
- Noted a study stating that the use of NRT for purposes other than smoking cessation was fairly common, where approximately one-third of the smokers that had used NRT within the past year had used it for reasons other than smoking cessation. The reasons included temporary abstinence or reducing the number of cigarettes smoked.
- Asserted that improper or haphazard use of NRT, which was more likely to occur in the absence of professional advice, could lead people to believe the NRT was not a useful/effective measure in quitting smoking.
- Asserted that after-hours access was comparable between the pharmacy and grocery sectors. Stated that there were no controls in place in the grocery sector to ensure quality use of medicines.

EXPERT ADVISORY COMMITTEE DISCUSSION

Oromucosal strips

Members agreed that the oromucosal strips had an equivalent risk/benefit profile to other forms of NRT currently available as unscheduled. A Member asserted, and the Committee generally agreed, that due to the harm to public health associated with tobacco smoking, broad availability of such forms of NRT should be supported to assist the public in quitting tobacco smoking.

A Member raised concerns regarding accidental use of these strips by children and non-smokers. The Member queried whether the presentation of the strips would resemble other confectionery strips currently available in supermarkets (e.g. oral mouth freshening strips) leading to their inadvertent use. However, Members noted that the nicotine strips would be packaged in a carton similar to other NRT forms currently available and the strips would be individually sealed to avoid inadvertent duplication of dose. Members agreed that the risks of inadvertent use of this NRT by children and non-smokers were low.

Members agreed to recommend to the delegate that nicotine oromucosal strips when used therapeutically as an aid in withdrawal from tobacco smoking should be exempt from scheduling.

Inhalation cartridges for oromucosal use

Members noted that the term "inhaler" could be misleading with regard to the product under consideration as it incorrectly implied that the nicotine dose was inhaled through the lungs instead of absorbed through the oral mucosa. The Committee agreed that the term "inhalator", as used by NZ, was a better descriptor of the presentation.

A Member raised concerns regarding the similarity of the inhalator and other products containing nicotine for inhalation which were not approved for human therapeutic use by the TGA. Members noted reports of misuse of nicotine vaporiser products (e.g. e-cigarettes). Members noted that unlike the inhalator, e-cigarettes visually resembled a cigarette. Members also noted e-cigarettes delivered nicotine through a vaporising system where it would be primarily absorbed through the lungs. In contrast, delivery of the nicotine dose via the inhalator facilitated absorption through the oral mucosa.

A Member asserted that, as with oromucosal strips, increased access to NRT oromucosal inhalators should be supported. The Committee generally agreed that the exemption from scheduling should be extended to oromucosal inhalators containing nicotine when used therapeutically as an aid in withdrawal from tobacco smoking.

Members noted that the current Schedule 2 entry for nicotine for inhalation was intended to capture oromucosal inhalators and not nicotine vaporiser products (e.g. e-cigarettes). Members clarified that e-cigarettes should be captured by Schedule 4 when for human

therapeutic use or by Schedule 7 if for non-therapeutic use. Members noted that apart from the oromucosal inhalators there were no other nicotine 'inhalation' products listed on the ARTG. Members agreed that it would be appropriate to delete the Schedule 2 entry for nicotine.

General oromucosal use

A Member queried whether the exemption from scheduling should be extended to all oromucosal forms of NRT. Members discussed the risks of new inappropriate forms of oromucosal products being developed. However, a Member reiterated that as all new NRT products would be assessed as part of the TGA registration processes, the risks of inappropriate NRT presentations being available as unscheduled products were low. Members generally agreed that the exemption from scheduling should be extended to all oromucosal use of nicotine when for human therapeutic use.

Members again confirmed that this general exemption for nicotine human therapeutic preparations for oromucosal use was not intended to extend to products which deliver the nicotine dose through a vaporising system (e.g. e-cigarettes). To ensure clarity, Members agreed that a definition of "oromucosal" should be included in the SUSMP. There was general discussion regarding the wording of this definition. Members agreed that reference to "the oral mucosa, specifically the oral cavity and/or the pharynx" best reflected the intent of this entry.

Implementation date

Members discussed appropriate implementation timeframes for this decision. Members noted that as the decision would reduce controls on new and existing products, a short implementation period of no more than 6 months would be appropriate.

DELEGATE'S INTERIM DISCUSSION

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

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

DELEGATE'S INTERIM DECISION

The delegate decided to extend the exemption from scheduling for nicotine in preparations for human therapeutic use to include all oromucosal use (i.e. would essentially harmonise with the New Zealand scheduling of nicotine for human therapeutic use). The delegate also decided that a definition of 'oromucosal' be included in SUSMP Part 1, Interpretation.

The delegate further decided to delete the Schedule 2 nicotine entry (i.e. nicotine inhalation cartridges for oromucosal use as an aid in withdrawal from tobacco smoking would be exempt and any other nicotine inhalation preparations for human therapeutic use will be captured by Schedule 4).

The delegate decided on an implementation date of 1 January 2012.

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate decided to extend the exemption from scheduling for nicotine in preparations for human therapeutic use to include all oromucosal use (i.e. would essentially harmonise with the New Zealand scheduling of nicotine for human therapeutic use). The delegate also decided that a definition of 'oromucosal' be included in SUSMP Part 1, Interpretation.

The delegate further decided to delete the Schedule 2 nicotine entry (i.e. nicotine preparations such as existing inhalation cartridges for oromucosal use as an aid in withdrawal from tobacco smoking would be exempt and any other nicotine inhalation preparations for human therapeutic use would be captured by Schedule 4).

The delegate decided on an implementation date of 1 January 2012.

PART 1 – INTERPRETATION – New entry

1. (1) …

"**Oromucosal**" means the oral mucosa, specifically the oral cavity and / or the pharynx.

Schedule 2 – Amendment

NICOTINE – Delete entry.

Schedule 4 – Amendment

NICOTINE – Amend entry to read:

NICOTINE in preparations for human therapeutic use **except** for use as an aid in withdrawal from tobacco smoking in preparations for oromucosal or transdermal use.

2.1.3 ORPHENADRINE AND PARACETAMOL COMBINATION

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

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

Orphenadrine – proposal to reschedule orphenadrine from Schedule 4 to Schedule 3 when combined with paracetamol with certain conditions. These conditions could include:

- limited orphenadrine content per dosage unit, such as 35 mg or less;
- a limited pack size, such as 24 dosage units or less; and/or
- a restricted indication, such as when used for the relief of pain associated with skeletal muscle spasm in adults and children over 12 years of age.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current scheduling of orphenadrine remained appropriate i.e. orphenadrine remains Schedule 4, including when combined with paracetamol.

BACKGROUND

Orphenadrine is a congener of diphenhydramine. It is a tertiary amine antimuscarinic agent with weak antihistaminic and local anaesthetic properties, and also inhibits noradrenaline transport and blocks NMDA receptors and voltage-gated sodium channels. The mechanism of its muscle-relaxing activity was unknown but probably related to an action within the CNS. Combinations of orphenadrine with an NSAID (usually diclofenac), or with paracetamol, have been used in the treatment of musculoskeletal and joint disorders.

Orphenadrine has been in use in Australia for about five decades as a prescription only muscle relaxant, both as a single component product (100 mg) and in a fixed dose combination with paracetamol (35 mg orphenadrine).

In February 2009, the NDPSC noted the withdrawal of an application to reschedule orphenadrine XXXXX.

SCHEDULING STATUS

Orphenadrine is currently listed in Schedule 4. It is a prescription medicine in New Zealand (NZ).

Preparations containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine, effervescent agents or guaiphenesin) in packs of 25 dosage units or less are exempt from scheduling (when compliant with labelling,

packaging and age restrictions). However, such preparations become Schedule 2 if combined with another therapeutic active. In the case of orphenadrine, the Schedule 4 status of the orphenadrine component would make an orphenadrine+paracetamol combination Schedule 4.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX requested the rescheduling of orphenadrine from Schedule 4 to Schedule 3 when compounded with paracetamol in oral preparations containing 35 mg or less of orphenadrine per dosage unit in packs containing 24 or less dosage units and when used for the relief of pain associated with skeletal muscle spasm in adults and children over 12 years of age.

The applicant's rationale for the rescheduling request has been summarised below:

- The combination of orphenadrine (a skeletal muscle relaxant) with paracetamol (an analgesic) would be useful where pain was associated with skeletal muscle spasm as the two components would relieve the two defining symptoms of the targeted indication.
- This combination (specifically orphenadrine citrate 35 mg and paracetamol 450 mg) had been available in Australia as a Schedule 4 medicine for over 30 years. This product was well established with a known efficacy and safety profile. The combination had been shown to provide effective relief in conditions such as musculoskeletal spasm, sports injuries, lower back ache and muscle contraction headaches.
- The proposed indication was readily recognisable by the consumer, generally self-limiting and suitable for short-term OTC treatment under the supervision of a pharmacist.
- The proposed combination would add to the currently available treatments for painful musculoskeletal conditions, providing a specific treatment for muscle spasm while avoiding the risks associated with non-steroidal anti-inflammatory drugs (NSAIDs).
- Treatment of muscle spasm would allow avoidance of immobilisation and consequential loss of work and other activities of daily living.
- Adverse effects were mainly due to the dose-related anticholinergic effect of orphenadrine, which were mild and could be managed by reducing the dose.
- There was over 45 years of global post-marketing surveillance with orphenadrine and its safety profile was comparable to that of other OTC medicines with anticholinergic activity. The combination formulation had been available in up to 64 countries, including as an OTC product in South Africa since 1978.

- There was a low level of relative risk associated with the rescheduling of orphenadrine given that many products with anticholinergic activity were listed in Schedule 2.
- Several factors, including pack size restriction, warning and precautionary statements in the PI, CMI and carton labelling, and the mandatory involvement of a pharmacist at point of sale would help to minimise the potential for adverse effects and misuse.

The applicant also provided specific claims against section 52E of the *Therapeutic Goods Act 1989*, as summarised and discussed under the Evaluation Report section.

Evaluation Report

Recommendation

The evaluator recommended that the application for rescheduling of orphenadrine to Schedule 3, when combined with paracetamol in a pack containing a maximum of 24 dosing units, be rejected.

Summary of reasons for evaluator's recommendation

- There was modest evidence for efficacy of the combination and of orphenadrine itself in mild, acute musculoskeletal injury.
- Safety of the combination was comparable to that of other anticholinergic medicines, and orphenadrine caused the usual range of adverse effects including dry mouth, palpitations, urinary retention, constipation, and confusion and dizziness in elderly people.
- The proposed pack would have child-resistant packaging and would provide only enough doses for four days of treatment; however, ingestion of more than about six tablets could cause significant toxicity in a child, with both components potentially contributing.
- The evaluator had significant concerns about the incompatible pharmacokinetics of the two components. Paracetamol reaches peak concentrations at about 45 minutes and declines with a half-life of about 2 hours, thus requiring dosing about every 4 hours to maintain a therapeutic concentration. Orphenadrine, however, was slowly absorbed, reaching a peak at about 4 hours and declining with a half-life of about 20 hours, thus requiring dosing every 12 – 24 hours. The recommended dosing schedule of the product was three times daily, representing a compromise between the two.
- This fundamental incompatibility in their pharmacokinetics meant that this combination was potentially unsafe. To achieve the effect of the paracetamol, the orphenadrine component needs to be dosed at an interval that will lead to considerable accumulation over a few days. Since its anticholinergic effects were dose-related, elderly consumers in particular would be put at risk of confusion, dizziness and subsequent falls.

Other conclusions

- The indication "relief of pain associated with skeletal muscle spasm" was suitable for Schedule 3 OTC treatment in that it could be diagnosed by consumers and appropriate treatment could be purchased with the assistance of a pharmacist.
- Orphenadrine in this dosing regimen had been shown to be effective (albeit in a small number of studies) and safe in the treatment of musculoskeletal pain, and would be suitable for availability as a Schedule 3 medicine.
- The original approval of the combination (as Schedule 4) appears to have occurred before the current system of regulation was implemented, and it seems to have been "grandfathered" onto the Australian Register of Therapeutic Goods. Although decisions about registration were not within the remit of the ACMS, the evaluator suggested that it would seem unwise to make this combination more readily available.
- The evaluator noted that, given the well-established place of paracetamol as a general sales medicine for short-term analgesia, and that the application was for rescheduling of orphenadrine, information concerning paracetamol had only been considered in relation to its presence in the combination.

Summary of evaluation of applicant's specific claims against section 52E

(a) Risks and benefits

Benefits

- The application included two evidence-based reviews of skeletal muscle relaxants; both concluded that the quality of the evidence supporting efficacy of orphenadrine was poor. A 2004 review concluded that there was "fair evidence" that orphenadrine was effective compared to placebo in patients with musculoskeletal conditions. Placebo-controlled trials of orphenadrine were identified in this review. In summary:
  - Three double-blind controlled trials were presented, two of which included a treatment arm relevant to orphenadrine+paracetamol.
  - The combination performed statistically significantly better than paracetamol alone and placebo.
  - Adverse effects were more common in the combination group, particularly in relation to stomach pains and drowsiness.

Risks

- The application contained no direct evidence regarding the therapeutic index of orphenadrine, although it claimed that the toxicity level in adults was between 1 and 4.5 g, and therefore deliberate misuse or overdose should not be dangerous in relation to the orphenadrine content (total pack content – 24 tablets – was 840 mg orphenadrine).
- Reports of orphenadrine overdose in the literature included:

- An ingestion of 4000 mg in an adult, which resulted in rhabdomyolysis, generalised convulsions and impaired consciousness, with a full recovery with supportive treatment; and
- A report of central anticholinergic syndrome, resulting in hallucinations and severe agitation, in a 3 year old after ingestion of 200 mg.

Thus ingestion of 6 tablets of the combination by a young child could result in significant toxicity from both the orphenadrine and the paracetamol components.

· Although a pack of the proposed combination contained less paracetamol than was present in packs of paracetamol-only products that were general sales items, the content of paracetamol was still sufficient to cause significant hepatic toxicity or death, even in an adult, if all of the contents were ingested at once.

(b) The purpose for use and extent of use

· Was to be used for the short-term self-management of acute musculoskeletal conditions. XXXXX
  - XXXXX

· XXXXX

· Reiterated the long history of marketing of orphenadrine-containing products. In 2010, XXXXX packs of the prescription combination were sold in Australia, indicating that usage was relatively infrequent.

(c) Toxicity and safety of the substance

· Periodic Safety Update Reports (PSURs) and ADRAC reports were reassuring as the number of adverse effect reports was only a small proportion of the number of people likely to have consumed orphenadrine (discussed in more detail under the summary of evaluation against SPF Schedule 3 factors below).

· However, no comparative information was available to allow an assessment of the severity of the anticholinergic adverse effects of orphenadrine compared with other anticholinergic drugs currently available as OTC medicines.

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

Rationale for a combination product

· The rationale for this combination, in terms of pharmacodynamics, was reasonable. It was also reasonable to consider combining a muscle relaxant with a simple analgesic.

· The applicant's argument that this combination met an unmet clinical need in OTC analgesia was based entirely on the pharmacodynamic argument, together with safety advantages over NSAIDs and opioids. The applicant also argued that taking one product rather than two would be more convenient.

- However, reiterated the concern that there was a significant pharmacokinetic problem in that the half-life of paracetamol was much shorter than that of orphenadrine. The evaluator particularly noted that although many of the monographs regarding orphenadrine quote a half-life of 14 – 16 hours, a recent pharmacokinetic study demonstrated very slow absorption (maximum concentration reached after 3 hours) and a mean half-life of 25.8 hours (range 15.3 – 59.5 hours). If dosed at 8 hourly intervals, it would be expected that orphenadrine would accumulate significantly for at least 5 days (5 half-lives).
- The pharmacokinetic profiles were described in the application as "differing yet complementary", on the basis that there were no pharmacokinetic interactions between them. The issue of the substantially different half-lives and the implications of this for dosing interval were not addressed. Members noted the applicant's specific discussion of this matter in the response to the evaluation report section.
- The evaluator argued that it would be much more appropriate and safer to administer orphenadrine and paracetamol separately, with dosing intervals of 24 hourly and 6 hourly, respectively. This would provide the pharmacodynamic advantages of the dual therapy without the risks associated with the very different half-lives.
- The evaluator also considered the expert report provided with the application. Although the expert dealt with all of the Schedule 3 factors and concluded that the combination product met all of the scheduling criteria, the expert had not addressed the pharmacokinetic incompatibility issue. The other points made in the expert report, including the suitability of acute muscular conditions for self-management, and the appropriateness of pharmacists as advisors to consumers purchasing drugs with anticholinergic properties, were accepted by the evaluator.
- The expert described the proposed educational program to be provided for pharmacists and agreed that this was appropriate.

Product packaging, labelling and CMI

- Because of the potential toxicity of the combination product for children, the product was to be presented in a child-resistant blister pack. The proposed labelling had been provided and the evaluator asserted that this was incomplete in that there were no cautions on the packaging in relation to use by elderly people, or the potential for the preparation to cause confusion.
- Given the association between advanced age and vulnerability to anticholinergic-induced confusion, which can result in serious falls and injuries, it could be argued that the CMI should include a caution in relation to the use of the product by elderly people. The CMI also omitted some precautions that were included in the PI; namely, that elderly people should be advised to take a reduced dosage because of susceptibility to anticholinergic adverse effects.

(e) Potential for misuse/abuse

- There was little, if any, evidence of abuse potential of orphenadrine.

Summary of evaluation against SPF Schedule 3 factors

The evaluator also reviewed the application in terms of the SPF's Schedule 3 factors. Many points were reiterations of those raised regarding the applicant's specific claims against section 52E and were not repeated. New points or additional details are summarised below:

Safety and need for pharmacist advice

- In relation to orphenadrine, the application provided upgraded safety data, including PSURs and an ADRAC Case Line Listing for orphenadrine:
  - The ADRAC Case Line Listing dated back to 1973 and included predominantly reports concerning the single-agent prescription form of orphenadrine (100 mg per dosing unit). No details were provided regarding the ingested dose in each case. The range of adverse events was broad, including visual disturbance, skin rash, and CNS features such as hallucination, extrapyramidal disorder, agitation and delirium, as would be expected for an anticholinergic drug. There were two reports for the orphenadrine+paracetamol combination, one of visual impairment and one of erythematous, pruritic rash.
  - The provided PSURs covered the period XXXXX . PSURs were first compiled for this drug in XXXXX, covering the period from XXXXX. The reports for the orphenadrine+paracetamol combination specifically included anxiety, deterioration of sight, dizziness, dryness of the mouth and kidney damage. Serious adverse effects included hallucinations and delirium, particularly in elderly people, sometimes resulting in falls and consequent injury.
- The reported exposure in terms of factory production of the combination was XXXXX. The total number of reports summarized in the most recent PSUR was XXXXX, the majority of which related to higher dose orphenadrine preparations.
- On balance, the indications and safety of orphenadrine 35 mg were consistent with this factor. Pharmacist involvement was required to warn consumers regarding the potential for anticholinergic adverse effects in particular. However, the recommended dosing interval was inappropriate given the half-life of the drug, and would result in accumulation and greater risk of anticholinergic adverse events.

Risk manageable by a pharmacist

- Reiterated that the risk profile had been well defined over a long period of time and that elderly consumers were at higher risk of anticholinergic adverse effects.
- Agreed that pharmacists would be appropriately equipped to identify and manage adverse effects and interactions. The major interactions of concern were with other drugs with anticholinergic properties (e.g. antihistamines and antidepressants).

Pharmacist intervention when intended for recurrent treatment of a chronic condition

- Noted that the indication for the combination was for a short-term treatment of an acute condition and therefore this factor was not relevant.

Potential to mask symptoms or delay diagnosis of a serious condition

- Given the proposed indication, the use of the combination would be unlikely to mask the symptoms of a serious condition related to skeletal muscle spasm, with one exception – tension headache. It would be possible, if the recommendations regarding dosing duration were not adhered to, for a consumer to suppress symptoms of a serious underlying condition causing headache. However, the pharmacist would be in a good position to detect any such inappropriate use.

Marketing experience

- Reiterated the previous discussion regarding the long market experience with both single-component orphenadrine and the combination with paracetamol.

Applicant's Response to the Evaluation Report

The applicant noted that the evaluator had focused on three main areas:

- Pharmacokinetics and appropriateness of the combination;
- Use of orphenadrine in elderly patients due to potential anticholinergic effect; and
- Potential outcome if the product might be ingested inappropriately or accidentally.

The applicant contested the concerns raised in respect to these areas – the applicant's arguments are summarised below:

Pharmacokinetics

- Argued that the evaluator's comments on the pharmacokinetics, in particular the half-life of orphenadrine, its potential for accumulation and implications for dose frequency, were not valid.
- Asserted that the evaluator's comments were at odds with the literature on the combination, the longstanding history of use and the substantial data from publicly available clinical study reports and formal post market reporting data.
- Endorsed the evaluator's comment that "The PSURs and ADRAC reports were reassuring in that the number of reports of adverse effects was a very small proportion of the number of people who were likely to have consumed orphenadrine". Reiterated that there was a verifiable safety track record based on longstanding PSUR and over 30 years of ADRAC data – the most recent 2 year period included XXXXX patient days of use. Argued that this, together with the publicly available data, was at odds with the evaluator's concerns regarding suitability and potential safety of the combination. Asserted that there was no safety related signal to suggest inadequate paracetamol dosing or significant orphenadrine accumulation that may increase risk of adverse effects.
- Noted that in a number of clinical trials the orphenadrine+paracetamol combination was used for longer periods than the 4 day supply proposed for Schedule 3. In

particular, studies of up to 17 months showed orphenadrine was well tolerated and, if anti-cholinergic effects occurred, they were in a minority of patients and self-limiting.

- Stated that 100 tablet packs have historically been available for prescription supply since registration in Australia over 30 years ago, to allow for potential treatment beyond 4 days. Asserted that this was consistent with treatment duration in various clinical studies and further testament to an absence of drug accumulation leading to greater risk of adverse clinical sequelae.

Orphenadrine dose within therapeutic blood levels

- Argued that it was highly unlikely that the orphenadrine component would accumulate after 4 or more days of therapy to result in potentially toxic blood levels of orphenadrine.
- The reduced orphenadrine amount in each dose of the combination would result in blood levels well within the therapeutic range for this drug from the pharmacokinetic study quoted by the evaluator. Noted that the study using 50 mg oral orphenadrine was the basis of the evaluator's comments about half-life and drug accumulation. The study found a maximum plasma concentration of 82.8+26.2 ng/mL, which was well within the 30-850 ng/mL therapeutic range for orphenadrine. It was also 24 times less than the reported 2000 ng/mL toxic level and 48-97 times lower than the 4000-8000 ng/mL lethal concentration for orphenadrine.
- Argued that the evaluator appeared to have not considered the many factors that could influence blood level concentrations, among which were the dose size.

Orphenadrine half-life

- Noted that the evaluator acknowledged "many of the monographs regarding orphenadrine quote a half-life of 14 – 16 hours", and that the study which was the basis of the evaluator's comments about half-life also recognised that the study's mean elimination half-life of 25.8 ± 10.3 hours was longer than that reported in previous papers.
- Asserted that the results of the longer half-life from this study, which the evaluator used as the basis for speculating on potential drug accumulation, should be interpreted with caution. Argued that to draw such conclusions was speculative because:
  - The key study purpose was to develop a sensitive assay method of determining plasma orphenadrine, after which PK assessment was performed.
  - The half life for orphenadrine was detected by the sensitive assay method developed, with unknown relevance. There was no evidence to suggest how much of this half-life phase contributed to steady state drug concentration nor the time it took to reach steady state. It may be that the shorter earlier half-lives from other studies were the dominant phases determining steady state parameters and which were relevant to orphenadrine's therapeutic effects.

- Noted again that the existing prescription product had over three decades of use in Australia without any safety signals or trends at the approved 3 times daily dosing regimen.
- Also, the study used orphenadrine hydrochloride, whereas the combination product contains orphenadrine citrate. These two salts were not interchangeable, with use for different indications, patient population, dosage and treatment duration.

Precedents – disparate pharmacokinetics in other Schedule 3 combinations

· The applicant was not aware of any regulation or guidance that required the half-lives of active ingredients to match in combination products.

· A relevant Schedule 3 precedent was analgesic preparations combining doxylamine 5 mg (an antihistamine with both anticholinergic and sedative/central nervous system effects), paracetamol 500 mg and codeine 8-10 mg. These three components have variable half-lives of 10 hours, 1-3 hours and 3-4 hours after oral dosing, respectively. Of relevance was that both a prolonged half-life of 15.5 hours and reduced drug clearance for doxylamine in elderly men had been shown and there were precautions in PI about this. However, the dose regimen for these longstanding Schedule 3 products was 1-2 tablets every 4-6 hours, if necessary, up to a maximum of 8 tablets in 24 hours for adults and children at least 12 years of age. This situation, whereby the dosing interval of the preparation was shorter than the half-life of doxylamine was similar to that of orphenadrine and provided further evidence that differing half-lives of active components could co-exist to provide an acceptable risk / benefit profile.

Paracetamol dosing adequacy

· Registered paracetamol products in Australia have a dose frequency varying from 0.5-1 g every 4-6 hours to 1.3 g three times daily. Paracetamol dosing in the combination product was 0.9 g three times daily, which provided a total daily dose of 2.7 g. This represents adequate paracetamol dose size and frequency. It was also within the range of total daily paracetamol consumed, i.e. 2-4 g, based on 0.5-1 g every 4-6 hours up to a maximum of 4 doses in 24 hours.

Suitability of the combination as Schedule 3

· Supported the evaluator's generally positive comments and conclusion that the indication was suitable for Schedule 3 OTC treatment and that orphenadrine at the proposed dosing regimen had been shown to be effective and safe in the treatment of musculoskeletal pain.

· Noted the evaluator's generally positive comments that:

- The proposed wording of the indications was generally satisfactory and was supported by the long history of marketing of orphenadrine-containing products.
- The PSURs and ADRAC reports were reassuring in that the number of reports of adverse effects was a very small proportion of the number of people who were likely to have consumed orphenadrine.

- The rationale for this combination in terms of pharmacodynamics was reasonable.

Legitimate use and risk

· In relation to overdose, the evaluator outlined two case reports. These both involved orphenadrine 100 mg tablets, rather than the 35 mg proposed for the Schedule 3 combination. The tablets were also taken under circumstances that did not represent legitimate use, summarised as follows:

  - One report of an adult who attempted suicide by purposely ingesting 40 x 100 mg orphenadrine citrate tablets. Although ingesting 4000 mg of drug, the person made a full recovery with supportive therapy. This was a deliberate act of intentional harm and a pharmacist would not supply the number of packs of the proposed OTC combination which would be needed for an individual to consume 4000 mg of orphenadrine. If, inconceivably, such a quantity was supplied, harm from paracetamol poisoning resulting in irreversible liver toxicity would be likely, although this would be much easier to achieve with unscheduled paracetamol only products available from general stores.

  - A report of a 3 year old boy who ingested 2 x 100 mg orphenadrine citrate tablets. The boy fully recovered in a supportive environment. The child had found the tablets in an easily accessed, unsuitable location in a sample container that lacked a child-safety enclosure. The applicant noted that the proposed combination would not be indicated for children less than 12 years and a child would have to swallow six tablets from a child resistant blister pack to ingest the same amount of orphenadrine as occurred in this case.

· The total orphenadrine base in one pack of 24 tablets would be 490 mg. This amount was substantially less than the potentially lethal dose range of 2 – 3 g orphenadrine in adults which in turn was 49-74 times higher than the amount of orphenadrine contained in one dose (two tablets).

Minimising risk – packaging, labelling, CMI and education

· Noted that the proposed pack was limited to allow a maximum of 4 days supply, i.e. short term management, and would be in a child resistant blister pack.

· Reiterated that the product would contain less paracetamol than other OTC paracetamol preparations.

· Reiterated that a dedicated educational support program for pharmacists would be provided by the applicant and the Pharmaceutical Society of Australia.

Anti-cholinergic effects versus other OTC preparations

· Noted the evaluator's statement that the safety of the combination was comparable to that of other anti-cholinergic medicines, yet the evaluator repeatedly raised the issue of anti-cholinergic effects related to the elderly.

· The applicant asserted that there was no greater risk of harm from the combination than from other products containing an anticholinergic agent or paracetamol, many of

which were Schedule 2 and unscheduled products. Indeed, there may be less risk of harm than these freely available products because of required pharmacist intervention.

- Specifically noted the example of doxylamine, a sedating antihistamine with anti-cholinergic effects contained in various Schedule 3 combination analgesics and also as a single active component in Schedule 3 products for the short-term management of insomnia. The PI for doxylamine, when used as a sleeping aid, warns of a prolonged half life and of studies indicating a longer duration of action, especially in elderly men. Given that codeine was present as an active ingredient in some Schedule 3 analgesic preparations containing doxylamine and both these agents have sedative and other CNS effects, argued that there was considerably greater potential risk of adverse events, particularly in the elderly, than for orphenadrine.
- Reiterated that the proposed combination was both codeine free and NSAID free, which were key advantages over other OTC analgesic preparations – an especially important aspect for the elderly.

Paracetamol content

- Noted that the total daily amount of paracetamol was in keeping with recent US Food and Drug Administration (USFDA) action to set new dosage limits for paracetamol to minimise the risk of severe liver injury from overdosing.
- Noted the evaluator's agreement that there was less paracetamol in one pack than in other general sale paracetamol only products. Reiterated the evaluator's comment on the adverse consequences of paracetamol overdosing by ingesting all the contents of a pack would also apply to all paracetamol containing preparations available in Australia.

June 2011 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX, both supporting the proposal. In addition a large number of identical form letters were received from pharmacists in support of the proposal (215 received by the closing date for submissions, 7 received late).

Members noted the following particular points from the pre-meeting submissions:

XXXXX

Summary of arguments in terms of section 52E

(a) Risks and benefits

- Argued that many consumers who take non-prescription analgesics self-treat because they do not know of alternative options.
- Asserted that the availability of a Schedule 3 analgesic with muscle relaxant actions would increase the scope of conditions with which a pharmacist could assist patients. It would also facilitate pharmacist intervention to enquire about the patient's pain

control with an opportunity to review analgesic use and assess whether the patient was taking the most appropriate therapy.

- Because orphenadrine shows some anticholinergic activity, it was contraindicated in patients with glaucoma, prostatic hypertrophy, obstruction at the bladder neck or myasthenia gravis. It may impair a person's ability to drive or operate machinery and should be used in caution in patients with tachycardia, cardiac decompensation, coronary insufficiency and cardiac arrhythmias.
- The contraindications and precautions were very similar to a number of antihistamines with anticholinergic activity that were listed in Schedule 3. Pharmacists were well placed to make the necessary enquiries to assess whether these antihistamines were safe to use and they should not experience any additional difficulty in assessing the situation for orphenadrine.

(b) Purpose and extent of use

- Back pain, back problems and disc disorders were very common in Australia, affecting around 2.8 million people. Of the reasons reported for seeing general practitioners, 2 per cent were for back complaints and 1 per cent were for headaches.
- Reiterated the long history of Australian use (as Schedule 4). Orphenadrine was effective compared to placebo in patients with musculoskeletal conditions (primarily acute back or neck pain) and a 1991 review demonstrated superior efficacy from a combination of orphenadrine and paracetamol than with paracetamol alone or placebo.
- The availability of a Schedule 3 combination product would enhance the capacity of community pharmacists to support patients who may present with lower back pain, tension headache and other acute and traumatic painful musculoskeletal conditions.

(c) Toxicity

- Side effects were mostly associated with the anticholinergic effects and were rare at the recommended dose, consisting primarily of nausea, dry mouth or blurring of vision. Rash or drowsiness may rarely occur and symptoms disappeared with dose reduction or cessation of treatment. No toxic effects had been reported.
- Asserted that the greatest risk with inappropriate use of combination products containing paracetamol was paracetamol toxicity. This risk was enhanced by the unrestricted availability of paracetamol through the grocery sector. Patients must rely on identifying the active ingredients of all the medicines they take.
- For the proposed combination, this risk would be somewhat mitigated by being Schedule 3 as pharmacists were familiar with the risk and experienced in counselling patients.
- Orphenadrine was a category B2 with regard to safety in pregnancy i.e. only limited information available but studies to date did not indicate any harm. As there were no data available regarding excretion into breast milk, it was recommended not to be used when breast-feeding. Again, these risks would be mitigated if the product was

Schedule 3 as pharmacists could advise pregnant or breast-feeding women appropriately.

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

- If orphenadrine+paracetamol was made available without prescription, Schedule 3 was the most appropriate category. This ensured that the product would be packaged and labelled to facilitate patient understanding of use and safety considerations, reinforced by pharmacist counselling.
- Again reiterated the long history of use of the combination. Long experience with the established dosing regime indicated that it was reasonable that packs of up to 24 dosage units would meet the requirements for Schedule 3. Resupply would require a pharmacist assessment with an opportunity for referral if appropriate.
- Drew attention to guidelines published by the Pharmacy Board of Australia which advised that, unless there were exceptional circumstances, only one package of Schedule 2 or Schedule 3 products should be supplied at any one time.
- As orphenadrine may affect a person's ability to drive or operate machinery and this risk was greatest for people who take the medicine on demand rather than regularly, appropriate warnings should be included on the product label. This would provide effective backup to pharmacist counselling.

(e) Potential for abuse

- There was a potential for anticholinergic medicines to be misused. Information about recreational effects of orphenadrine had been documented, and was similar to the risk associated with other non-prescription medicines with anticholinergic properties, including diphenhydramine, dicylomine, pheniramine and scopolamine.
- Was concerned with the potential abuse of all of these medicines, but believed this could be managed. Pharmacies accredited under the Quality Care Pharmacy Program (QCPP) have systems in place to monitor and manage the supply of non-prescription medicines that may be subject to inappropriate use.
- Schedule 3 medicines must also be stored such as to prevent public access, and to be supplied when the pharmacist has assessed appropriate and safe use. Asserted that, while not fool-proof, this went a considerable way in managing the abuse potential.

(f) Other matters

- While there were concerns with consumer health-literacy for all medicines, access to Schedule 3 medicines facilitates counselling by a pharmacist which augments written cautions and instructions included on a product's label.
- Generally did not support restricted indications as part of the scheduling process as this complicates SUSMP listings. Instead argued that restricted indications should be managed as part of the registration process so that the product could be labelled with appropriate instructions and marketed accordingly.

XXXXX and the pharmacist form letters

- Advised that, following publication of the pre-meeting notice, it was in possession of over 200 letters from Australian pharmacists expressing the opinion that the proposed orphenadrine+paracetamol combination should be accessible to pharmacists as an alternative OTC option for painful musculoskeletal conditions, which could support Quality Use of Medicines, given these benefits:
  - was the only OTC product containing a skeletal muscle relaxant;
  - was codeine, opioid and NSAID free; and
  - was an alternative to benzodiazepines.
- The letters stated that orphenadrine+paracetamol would help pharmacists to better support individuals presenting with lower back pain, tension headache and other various acute and traumatic painful musculoskeletal conditions.
- The letters also stated that pharmacists were well equipped to assess the benefits and risks of this combination and make recommendations for its appropriate use.
- Reiterated that it was committed to ensuring that thorough education and pharmacy protocols for supplying and recommending orphenadrine+paracetamol were in place.
- Asked that the collective sentiment expressed by these pharmacists be considered.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members first considered the incompatible pharmacokinetics concerns raised by the evaluator in light of the rebuttal arguments from the applicant. Members noted that a number of existing Schedule 3 combination products containing other active ingredients had a comparatively more significant incompatible pharmacokinetics issue. Some Members maintained that this remained a real concern, while others asserted that advice from a pharmacist should be sufficient to mitigate any such risk.

A Member asserted that there appeared to be limited demand or desire for orphenadrine which was not a highly prescribed substance despite all its years as Schedule 4. The Member also asserted that it had only modest evidence of efficacy. Another Member noted that TGA had approved the Schedule 4 product, indicating a positive efficacy finding. Several Members suggested, however, that it was likely that the Schedule 4 orphenadrine products had been grandfathered into the Australian Register of Therapeutic Goods.

Several Members also noted that orphenadrine had CNS effects and that muscle relaxants must be used with caution due to their potential for misuse. Members noted that there existed US FDA reports of associations of orphenadrine with substance abuse. A Member maintained that the Committee should be wary of any moves to add additional OTC products to the market which may be subject to abuse, particularly given the orphenadrine+paracetamol combinations' modest evidence of benefit.

A Member argued that in light of its asserted limited benefits, the acceptability of the combination's side effect profile (particularly the anticholinergic effects) and its various contraindications in an OTC product was diminished. The Member also noted that the toxicity of just six of the proposed tablets could be significant in children. Several Members agreed that there appeared to be insufficient evidence of benefit, given the concerns (especially to the elderly), to warrant down scheduling of orphenadrine when in combination with paracetamol.

A number of Members agreed that there may be a need for a Schedule 3 medicine of this type (i.e. a combination of a skeletal muscle relaxant with an analgesic) but felt that orphenadrine+paracetamol did not appropriately fulfil this need.

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; (c) toxicity; and (e) potential for abuse.

DELEGATE'S INTERIM DECISION

The delegate decided that the current scheduling of orphenadrine remained appropriate i.e. orphenadrine remains as Schedule 4, including when combined with paracetamol.

SUBMISSIONS ON INTERIM DECISION

One further submission was received from XXXXX (the applicant) opposing the interim decision and reiterating its requested inclusion of the proposed orphenadrine+paracetamol combination in Schedule 3. The submission also made several points, as summarised below:

XXXXX

- Reiterated that the orphenadrine+paracetamol combination with the proposed dosing regimen and pack size was both effective and safe in the treatment of musculoskeletal pain. Asserted that the body of evidence also showed an acceptable benefit-risk profile for the combination. Reiterated the length of use of the combination, globally.
- Asserted that the TGA approved the Schedule 4 product and through this indicated a positive efficacy finding. Reiterated the evaluator's comments in relation to the substance's safety and efficacy.
- Agreed with a Member's comment that the combination's pharmacokinetics were not as incompatible as some other existing Schedule 3 medicines. Noted the evaluator's notes on the combination's safety and adverse effects and stated that these statements

were supportive of Schedule 3 inclusion and that pharmacist intervention would be sufficient to mitigate any potential risk as a Schedule 3 medicine.

- Disagreed with a Member's comment regarding limited demand for the combination and asserted that the PSUR reports indicated widespread global use. Asserted that until recently the combination's sponsors had not actively promoted this product, therefore prescribing had not been high in Australia.
- Noted comments contained in the delegate's published reasons regarding the combination's safety and potential for misuse. Asserted that orphenadrine (as the hydrochloride salt) has been used for many years for the treatment of Parkinson's Disease in elderly patients at doses higher than the recommended dose of the proposed combination without an increase in reported adverse effects.
- Noted that older consumers were more vulnerable to adverse effects and reiterated that if the combination was downscheduled the pharmacist would mitigate potential risks associated with the combination through assessment and advice.
- In relation to a Member's comment regarding associations of orphenadrine with substance abuse, asserted that studies and global post-market experience do not correlate or support the US FDA reports. Stated that post-market surveillance data and clinical studies did not support any abuse issue associated with orphenadrine. Noted that there were differences in the formulation, dose strength and pack size of orphenadrine products in the US compared to the proposed Australian combination. Noted the evaluator's remarks regarding a lack of evidence of abuse potential of orphenadrine.
- In relation to a Member's comments regarding potential toxicity in children, asserted that the combination presented no greater risk of toxicity than other current Schedule 3 medicines. Compared the proposed combination to packsizes of currently unscheduled paracetamol products.
- Agreed with the Committee's comment regarding the potential need for a combination skeletal muscle relaxant and analgesic product. Argued that the orphenadrine+paracetamol combination fulfilled this need as it was the only product containing a skeletal muscle relaxant and low level analgesic, an alternative option to benzodiazepines, codeine and opioid free and NSAID free.

DELEGATE'S RECONSIDERATION OF INTERIM DECISION

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

The delegate agreed that the interim decision was appropriate and that orphenadrine when combined with paracetamol should remain as Schedule 4.

DELEGATE'S FINAL DECISION

The delegate decided that the current scheduling of orphenadrine remained appropriate i.e. orphenadrine remains as Schedule 4, including when combined with paracetamol.

2.1.4 COUGH AND COLD PREPARATIONS

Note: The delegate's interim decision on cough and cold preparations was made following consideration of ACMS advice from the December 2010 and June 2011 meetings. This record outlines the delegate's referrals for advice, pre-meeting submissions and ACMS discussion from each of these meetings.

Parties who made a valid submission for consideration at either meeting are invited to make further submissions on the interim decision below.

BACKGROUND

TGA Review of Cough and Cold Medicines

In 2008-2009, the TGA, through its Cough and Cold Medicines Review Panel with the assistance of external medical experts and the then Medicines Evaluation Committee – MEC (now replaced by the Advisory Committee on Non Prescription Medicines – ACNM), reviewed the safety, efficacy, availability and packaging of OTC cough and cold medicines registered in Australia for use in the symptomatic treatment of children aged 2 to 12 years.

In brief, the Review:

- Concluded that there was no robust evidence of efficacy for any of these drugs for the symptomatic treatment of coughs and colds, and that use of these drugs constituted a safety risk to children, especially those aged less than 6 years.
- Recommended that all OTC cough and cold medicines should be in child-resistant packaging.
- Sought and obtained stakeholder and public submissions which the TGA Panel took into account in formulating its final conclusions.
- Noted that similar reviews were also carried out by the medicines regulatory authorities in the UK, USA, Canada and NZ with the same conclusions being reached about safety and efficacy of these medicines in the treatment of children.

The TGA, in initially referring the Review for scheduling consideration, recommended the following scheduling cascade for cough and cold substances (except codeine, dihydrocodeine and pseudoephedrine, for which the TGA asserted that the current scheduling was appropriate):

Schedule 2 adults and children above 12 years

Schedule 3	children aged from 6 to 11 years
Schedule 4	children under 6 years

The TGA also stated that ammonium salts could remain unscheduled since, when used in cough and cold medicines, they were normally compounded with other substances that would be scheduled.

Scheduling considerations

In June 2010, the NDPSC considered and only partially endorsed the TGA's recommendations, instead agreeing that the following cascade should apply only where it would not result in less restrictive scheduling:

Schedule 2	adults and children above 6 years
Schedule 3	children aged from 2 to 6 years
Schedule 4	children under 2 years

The NDPSC recommended that this rescheduling should only apply to the following substances for the treatment of cough and cold (the NDPSC agreed that the use of ammonia, bromhexine, and guaiphenesin in these preparations did not need to be rescheduled):

brompheniramine	diphenhydramine	promethazine
carbetapentane	doxylamine	pseudoephedrine
chlorpheniramine	ipecacuanha	senega
codeine	*oxymetazoline	triprolidine
dexchlorpheniramine	pheniramine	*xylometazoline
dextromethorphan	phenylephrine	
dihydrocodeine	pholcodine	

* Except when for nasal spray use.

However, this item was not finalised, in accordance with the agreed transition arrangements for matters considered concurrently with the implementation of revised scheduling arrangements from 1 July 2010. Instead, the NDPSC referred the above recommendations to a delegate under the revised scheduling arrangements. The delegate in turn referred the NDPSC recommendations to the December 2010 ACMS meeting for advice.

In December 2010, the ACMS agreed with the NDPSC-proposed cascade with a number of exceptions: that the proposed scheduling not apply to phenylephrine or carbetapentane

in cough and cold preparations in adults and children 12 years of age and over; and that senega should remain unscheduled.

> ** Members' discussion at the December 2010 ACMS meeting and a summary of the material considered is provided under the "December 2010 ACMS consideration" heading below.

A delegate noted the ACMS' recommendations and decided to seek further advice prior to making an interim decision on the matter. Following consideration of further TGA advice, the delegate referred a revised proposal for five cough and cold preparations to the June 2011 ACMS meeting for advice.

> ** Resulting Members' discussion at this meeting and a summary of the material considered is provided under the "June 2011 ACMS consideration" heading below.

SCHEDULING STATUS

The majority of the substances considered by the TGA Review are included in Schedule 2, although a few are in Schedule 3, 4 or 8 depending on the strength or dosage and whether they are in single-active products or in combinations with specific substances. All sedating antihistamines for use in children under 2 years of age are Schedule 4 medicines.

Carbetapentane, guaiphenesin, ipecacuanha, phenylephrine and senega were the only substances recommended for consideration by the TGA Review which were available as unscheduled in some cough and colds medicines.

DECEMBER 2010 ACMS CONSIDERATION

DELEGATE'S REFERRAL TO DECEMBER 2010 EXPERT ADVISORY COMMITTEE

Cough and cold medicines – proposal to reschedule 19 substances used in over-the-counter cough and cold medicines to:

- Schedule 4 for use in children less than 2 years of age.
- Schedule 3 for use in children aged from 2 to 6 years of age.
- Schedule 2 for use in children and adults above 6 years of age.

The delegate proposes that this rescheduling apply to the following substances for use in cough and cold products (only where it will not result in less restrictive scheduling):

Brompheniramine	Oxymetazoline (excluding for nasal spray use)
Carbetapentane	Pheniramine

Chlorpheniramine	Phenylephrine
Codeine	Pholcodine
Dexchlorpheniramine	Promethazine
Dextromethorphan	Pseudoephedrine
Dihydrocodeine	Senega
Diphenhydramine	Triprolidine
Doxylamine	Xylometazoline (excluding for nasal spray use)
Ipecacuanha	

This proposal is a result of recommendations from the June 2010 meeting of the NDPSC following consideration of a review of cough and cold medicines by the TGA.

DECEMBER 2010 EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended:

- That the use of certain substances in preparations for the treatment of cough and cold be rescheduled to:
  - Schedule 4 for use in children under 2 years of age;
  - Schedule 3 for use in children from 2 to 6 years of age (inclusive);
  - Schedule 2 for use in adults and children over 6 years of age.
- that this rescheduling apply to brompheniramine, carbetapentane, chlorpheniramine, codeine, dexchlorpheniramine, dextromethorphan, dihydrocodeine, diphenhydramine, doxylamine, ipecacuanha (*Cephaelis acuminate* and *Cephaelis ipecacuanha*), pheniramine, phenylephrine, pholcodine, promethazine, pseudoephedrine, triprolidine, oxymetazoline and xylometazoline;
- that the above rescheduling **not** apply to oxymetazoline and xylometazoline when for nasal use for the treatment of cough and cold;
- that the above scheduling **not** apply to phenylephrine in cough and cold preparations for use in adults and children 12 years of age and over, i.e. no change to phenylephrine scheduling for use in adults and children 12 years of age and over; and
- that the above scheduling **not** apply to carbetapentane in cough and cold preparations for use in adults and children 12 years of age and over, i.e. no change to carbetapentane scheduling for use in adults and children aged 12 and over.

The Committee also recommended:

- that the above rescheduling should apply only where it will not result in less restrictive scheduling;

- that senega should remain unscheduled; and
- an implementation date of 1 May 2012.

DECEMBER 2010 SUBMISSIONS

TGA's June 2010 submission to the NDPSC

ACMS Members noted the TGA request for the NDPSC to consider the following recommendations from the TGA Panel's review regarding substances in cough and cold medicines (except codeine, dihydrocodeine and pseudoephedrine, for which the TGA asserted that the current scheduling was appropriate).

- Schedule 2: if labelled with a warning stating that it not be used in children under 12 years of age. This would ensure that professional advice would be available but would not restrict supply for use in adults and older children and not unduly burden pharmacists with the need to deal personally with every sale of an OTC cough and cold medicine.
- Schedule 3: if labelled with warnings stating that it not be used in children aged under 6 years and should only be used in children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner. This would ensure that professional health advice was provided, including referral to medical practitioners.
- Schedule 4: in preparations for the treatment of children under 6 years of age. This would greatly reduce the usage of these medicines in young children, but would allow medical practitioners to prescribe them if necessary, particularly as treatment for an ailment other than common cough and cold.
- The TGA subsequently clarified that, in addition to the highlighted proposals for children, the body of the TGA Panel's review also recommended additional controls for adults and/or children aged 12 and above.

Main points from the TGA's request included the following.

- There was no robust evidence of efficacy for the identified active substances for the symptomatic treatment of cough and cold, and that use of these substances constituted a safety risk to children, especially those aged under 6 years.
- Public and stakeholder consultation was undertaken and responses considered.
- While the number of adverse events reported to the TGA may not be high, safety data from other countries with regulatory systems comparable to that of Australia (UK, USA, Canada and New Zealand) demonstrated a high rate of adverse events. Reviews by these regulators reached similar conclusions, i.e. when these substances were used in cough and cold medicines they constituted a safety hazard to children.

- While the current scheduling (mostly Schedule 2) ensured that advice about these products was available at pharmacies it did not guarantee that advice was actually given or that the advice was necessarily appropriate.
- Both labelling and scheduling needed to ensure that parents and caregivers were made fully aware of the lack of efficacy for the treatment of cough and cold and the risks involved in administering these medicines to young children.
- Changes to labelling requirements for these products to ensure that they carry clear warnings that they are not to be used in children aged under 6 years (rather than under 2 years as at present) and that they should only be used in children aged 6 to 12 years on the advice of a doctor, pharmacist or nurse practitioner. It was the TGA Panel's view that the scheduling of the substances concerned needed to reflect these proposed changes to the indications and labelling.
- Ammonium salts could remain unscheduled since, when used in cough and cold medicines, they were normally compounded with other substances that would be scheduled.

June 2010 NDPSC Discussion

ACMS Members noted the following summary of points made at the June 2010 NDPSC consideration of the 22 cough and cold substances:

Risk versus benefit

- A principal concern identified in the TGA Panel's review was the lack of efficacy of these substances in treating cough and colds. There was also some positive evidence of no efficacy in any age group, especially children, including results from a number of clinical trials.
- A Member noted, however, that the cited efficacy studies appeared to be mostly poor, with low numbers and little statistical power, and that this undermined to a degree the basis of the TGA Panel's conclusions. Another Member contested that the external report (which formed part of the basis of the TGA's review) drew on a Cochrane assessment which found no evidence "for or against" efficacy rather than "positive evidence of no efficacy".
- A Member, while conceding that there was little evidence of efficacy, asserted that this should not be surprising as these were mostly old products where there had been no regulatory requirement or commercial reason to drive companies to undertake new studies. The Member asserted that, while acknowledging the lack of robust efficacy data, this should not be the basis for rescheduling. The Member observed that in recent considerations of codeine it was agreed that the issue of efficacy was best left to the regulator (as part of any product approval process) and that rescheduling was instead due to codeine misuse concerns. Other Members asserted that the codeine issue was a different situation (where efficacy was less central to the concerns given the clear risks of abuse). The Committee agreed that each issue needed to be assessed

on its own merits with regard to the relevance of efficacy to scheduling considerations.

- Some Members reiterated the query from one pre-meeting submission that, if there was no evidence that these products were efficacious, why were these products registered at all. Other Members argued, however, that deregistering would be an extreme response given the quality of the data and the low likelihood of serious AEs, and that a more reasonable compromise might be to consider more restrictive access through scheduling in the first instance, until better information became available.
- Several Members highlighted the low number of reported serious AEs (less than 3 per annum for children under 6 years of age in Australia). Other Members noted that AEs for OTC medicines were always strongly under-reported. A Member asserted that, while it was assumed that under reporting occurred, this was the conventional way to collect this data and therefore this information should be considered.
- A Member questioned this data and noted that the reported AE numbers did not identify how many of these occurred before the mandated child-resistant closure (CRC) requirements took effect for cough and cold preparations. Recent data from Poisons Information Centres seemed to indicate that less severe AEs were being reported, with serious AEs becoming increasingly rare since the introduction of the CRC requirement. The Member therefore suggested that the data presented in the TGA Panel's review may not reflect the current situation.
- A Member also asserted that, in addition to AE concerns, the current use of these products in children could mask symptoms and delay medical intervention. The Member argued that, especially for the very young, consultation with a doctor was often necessary to determine if a child was suffering from a more serious condition e.g. asthma.

Possible scheduling

- Members discussed the TGA Panel's recommended approach to cough and cold medicines for children – the proposed scheduling cascade, together with proposed regulatory action through changes to indications, labelling and packaging. Members particularly focussed the discussions on the proposed cut-offs based on age. A Member reiterated the likely off-label misuse of these products, as raised in a number of pre-meeting submissions, should access be differentiated on the basis of age.
- It was also clarified that in NZ, use in children under 6 was controlled largely through contraindications for this use, rather than by classification as a prescription only medicine. A Member suggested that this may be an appropriate approach for Australia to consider, noting that use in children under 2 years was already precluded, though not necessarily through scheduling (while this was the case for antihistamines, some other actives did not have current scheduling age cut-offs for OTC use). Members generally agreed, however, that it would be clearer for such controls to be reflected by a scheduling cascade.

Exceptions

- Members noted that, of the 22 substances identified in the TGA Panel's review, a number were recommended for exemption from the proposed cascade as it was considered that either existing controls were sufficient (codeine, dihydrocodeine and pseudoephedrine) or that scheduling was not necessary (ammonia). Various pre-meeting submissions also proposed that certain other substances (including bromhexine, guaiphenesin, oxymetazoline and xylometazoline) also be excluded from any rescheduling decision.
- A Member advised that in NZ, while the use of guaiphenesin in children under 6 was contraindicated, a change to the scheduling of cough and cold medicines that contained guaiphenesin only was not warranted as there was little reported risk from use of this substance in children aged 6 years and older. Additionally, there appeared to be better evidence of efficacy for guaiphenesin with no real safety issues.
- The NDPSC therefore agreed that guaiphenesin should not be included in the rescheduling action. Additionally, the NDPSC agreed with the TGA Panel's proposal that rescheduling of ammonia was not necessary.

December 2010 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX. Edited copies of these submissions were published in February 2011 at www.tga.gov.au/industry/scheduling-submissions-1012.htm.

The main conclusions from these submissions were as follows.

- XXXXX accepted the Schedule 3 and Schedule 4 rescheduling proposals by the NDPSC in June 2010. The proposal that use by adults and children 12 years of age and over should be Schedule 2 was not supported. It was argued that this proposal be revised so as to only apply to children from 6 to 12 years of age. XXXXX also supported this position.
- XXXXX also supported the Schedule 3 and Schedule 4 rescheduling proposals by the NDPSC in June 2010. They supported that the remaining use (adults and children over 6 years of age) should be Schedule 2, except for phenylephrine, arguing instead that certain phenylephrine preparations should continue to be available unscheduled for adults and children 12 years of age and over. This proposal was supported by XXXXX. XXXXX also sought extension of this to include carbetapentane.
- XXXXX was willing to accept that the rescheduling proposals would represent the best compromise between accessibility and safety that could be achieved for the substances considered.
- XXXXX supported the rescheduling proposals, however proposed that the exclusion of ammonium chloride, bromhexine and guaiphenesin be overturned to reduce confusion. These substances were not in the pre-meeting notice.

- XXXXX also suggested rewording the exclusion of oxymetazoline and xylometazoline for 'nasal spray use' to 'for topical nasal use' for greater flexibility and to ensure that other topical preparations, e.g. nasal drops), containing these substances would also be covered by the exclusion. XXXXX supported a similar rewording specifically for oxymetazoline, suggesting "for nasal use", again to account for nasal drops.
- XXXXX accepted the general proposal but argued that Schedule 3 should capture children from 2 years of age up to (but not including) 6 years of age, and that children 6 years of age should instead be captured in Schedule 2.

Members noted that there was a degree of inconsistency in submissions' terminology for age cut-offs. In relation to the labelling of a number of phenylephrine unscheduled products, the following terminology assumptions were made: the term "over 12" referred to 12 years of age (inclusive) and over and the range "2-12" referred to children from 2 years of age (inclusive) up to and including 11 years of age, but would not include 12 years of age. Members agreed that this appeared to be the correct interpretation given the context of the subsequent discussion on these submissions.

XXXXX noted that studies on cough and cold medicines representing approximately 95 per cent of the paediatric market were being undertaken in the US, and were expected to be completed in 2011. XXXXX proposed that the results of these studies should be considered prior to imposing further scheduling restrictions. XXXXX also noted the US studies, but argued that the proposed rescheduling should go ahead and that this could be subsequently reassessed and evaluated, i.e. when the US information became available.

The following table summarises the various proposed cascades from submissions (the differences from the NDPSC proposed rescheduling are highlighted in grey):

	NDPSC XXXXX	**XXXXX**	**XXXXX**	**XXXXX**	**XXXXX**	**XXXXX**
Schedule 2	> 6	≥ 6	> 6 to <12	> 6, > 6 to <12 for phenylephrine	> 6, > 6 to <12 for carbetapentane	NDPSC recommendations extended to ammonium chloride, bromhexine, guaiphenesin
Schedule 3	2 to ≤6	2 to <6	2 to ≤6	2 to ≤6	2 to ≤6	
Schedule 4	< 2	< 2	< 2	< 2	< 2	

Several submissions also commented on the timing of rescheduling decisions.

- XXXXX requested that the proposed changes be implemented in a reasonable fashion, especially given the lack of evidence of patterns of misuse, either intentional or accidental, or serious injury to children in Australia caused by current use of cough and cold medicines.

- XXXXX noted that the rescheduling proposals affect many medicines and that labelling changes to seasonal products such as these are especially complex.
- XXXXX suggested that the implementation of any labelling or scheduling changes be finalised in consultation with all stakeholders, having due regard to the number of affected products and the complexities involved.
- XXXXX requested that consideration be given to allow sponsors to run out existing product, as well as allow adequate time for implementation of any new label warnings. XXXXX requested consideration of a timeframe of 12-18 months for any decision.

Members also noted the following specific details from the pre-meeting submissions.

XXXXX

- Noted that the current scheduling of most cough and cold medicines as Schedule 2 medicines ensured that advice was available from a pharmacist, if necessary.
- Noted that cough and cold products have a long history of safe use in Australia in both adults and children and asserted that many products on the market have been available and used safely for more than 30 years.
- Contended that the proposal for restricting the use in adults and children over 6 years of age to Schedule 2 was outside the scope of the TGA Panel's review, arguing that this was therefore not justified on the basis of evidence available and would have unintended effects on the scheduling of products labelled for use in adults.
- Contended that some of the proposed changes were excessive and not justified on the basis of the evidence available and that it was important that the Australian scheduling of OTC cough and cold medicines continue to be aligned with NZ requirements.
- Provided a summary of the background to the issues which prompted the TGA Panel's Review, including the status of matters in the US and also provided a detailed summary of the background and context of the external report to the TGA Panel and three Cochrane reviews which were considered by the TGA Panel.
- Argued, with regard to the specific phenylephrine proposal (where Schedule 2 would only apply to children from 6 to 12 years of age), that this would prevent unintended effects on existing products labelled for use in adults which were unscheduled. In particular, it was noted that products containing paracetamol combined with phenylephrine and/or guaiphenesin were considered in February 2010 by the NDPSC. The NDPSC agreed that such combinations should be unscheduled if (among other things) they were not labelled for the treatment of children under 12 years of age. XXXXX argued that this decision was made specifically in the context of the TGA's review of cough and cold products.

- Reiterated their previous statement that any changes would need to be widely promoted and explained to medical practitioners, pharmacists, parents and caregivers. In particular, it would be very important to emphasise the long history of safe use of cough and cold medicines in Australia, both in adults and in children and to avoid causing undue concern or alarm by citing data relating to overseas use in circumstances where presentation and availability have been very different from the practice in Australia.
- Discussed specific matters under section 52(E) of the *Therapeutic Goods Act 1989*, summarised below.

(a) Risks and Benefits

- Reiterated previous arguments that cough and cold products have a long history of safe use in Australia in both adults and children. Mild, reversible side effects of cough and cold medicines are well known and well described.
- XXXXX.
- Noted that over a period of 28 years (1981-2009) the TGA had received 99 reports of suspected adverse drug reactions (ADRs) in children under 12 years of age associated with cough and cold medicines. Fourteen ADRs were classified as serious (1 probable causality, 10 possible, 3 unclear). Twelve of the serious ADRs occurred in children under 6 years of age. In addition, two reports of accidental overdose and two reports of intentional overdose were received.
- Argued that the TGA did not provide a yearly pattern breakdown of ADRs and so it was not possible to determine if ADRs had decreased (or increased) in recent years. Also asserted that this ADR data was not consistent with the statement that the TGA in making its recommendations considered "the historical profile of ADRs in Australia and overseas".
- Argued that the TGA's conclusion that "the risks relating to use of cough and cold medicines in children outweigh the benefits" was not justified.
- Noted that the external report to the TGA Panel stated that "death or serious injury from children's cough and cold medicines is vanishingly rare". Although there were a substantial number of calls to Poisons Information Centres (PIC) in regard to these medicines, very few were considered to be serious enough to refer for assessment and treatment. The external report also stated that it was possible to make the following definite conclusions.
    - Generally, these medicines were very unlikely to be harmful in label dosages, and in non-intentional overdose in the typical 1-2 year old age group, serious poisoning was rarely seen.
    - A recent study in the US demonstrated that OTC cough and cold preparations were only present in toxicology screens in 5 per cent of life-threatening poisonings in children.

- This may not apply to some drugs in adult doses in solid form, but this was not going to be influenced by any changes that might be made in the nature or availability of these medicines for children.
- Overseas reports of serious poisoning including deaths from cough and cold medicines were generally not reflected in current Australian experience. Documentation of such deaths was often confounded by co-existing severe illness, multiple drug administration, solid drug forms, the possibility of homicide and other factors.

- Noted that the terms of reference for the external review were limited to use in children aged under 12 years of age and argued that the external report to the TGA Panel demonstrated that the risks to children decreased with increasing age.

Efficacy

- Noted that the risk/benefit ratio of cough and cold preparations was difficult to ascertain, as stated in the TGA's Internal Report. The external report to the TGA Panel stated that it was impossible to make a general statement about the efficacy of the 22 cough and cold medicines for children which were reviewed, and death or serious injury from children's cough and cold medicines was rare.
- Stated that OTC cough and cold medicines, in common with many other existing therapeutic products, were "grandfathered" when the new national regulatory system was introduced in Australia in 1991. In general, there was currently insufficient evidence for or against the effectiveness of cough and cold medicines which meets modern standards for clinical trials.
- Noted that the Cochrane reviewers did not conclude that cough and cold medicines were ineffective, but concluded that there was insufficient evidence for or against their effectiveness which meets the standards and criteria applied by the Cochrane review.
- Stated that, in the external report to the TGA Panel, the external reviewers noted that "There is an undoubted strong demand for cough and cold medicines for children, interpreted by some as evidence of efficacy. The reviewers do not agree with this interpretation, but there is no evidence to refute or support the idea."
- Asserted that the proposed restrictions should be reviewed if and when robust efficacy data became available.

(e) Potential for misuse / abuse

- Asserted that given the absence of any evidence of abuse or misuse, it was unlikely that the proposed restrictions would have any impact on the potential for misuse.

XXXXX

- Summarised the current criteria for phenylephrine to be unscheduled (including when not labelled for children under 12 years of age) and reiterated XXXXX point that this was only recently considered and that the NDPSC was aware at that time of the work being done by regulatory authorities in Australia and overseas on the safety of cough and cold medicines in children 2 to 12 years of age.
- Noted that the delegate's proposal of "Schedule 2 – for use in children and adults over 6 years" [of age] was absolute and made no mention of the current exclusions continuing to be allowed.
- Reiterated XXXXX argument that the TGA's consultation process had been centred on the use and safety of actives in children 2 to 12 years of age.
- Argued that the rescheduling of phenylephrine to remove the existing use as an unscheduled medicine in adults and children over 12 years of age was not justified asserting that the TGA's evidence did not support tightening the scheduling of phenylephrine for use in this age group and that the safety of these products in adults and children over 12 years of age had not been questioned.
- Proposed that this could be done by amending part (b) of the current Schedule 2 phenylephrine entry (oral preparations containing 50 mg or less of phenylephrine per recommended daily dose in packs containing 250 mg or less of phenylephrine) to include when not labelled for use in children under 12 years of age.
- Asserted, with regard to additional labelling, that any new labelling warnings should be considered separately as part of the RASML requirements and should allow for flexibility in wording as well as consultation with industry.

XXXXX

- Agreed that the supply of these medicines for the treatment of children aged 2 to 6 years of age should be accompanied by the advice of a pharmacist, and that when supplied for the treatment of older children and adults, pharmacist advice should at least be available to the purchaser.
- Thanked the NDPSC for reconsidering its position in relation to ammonia, bromhexine and guaiphenesin, and oxymetazoline and xylometazoline when used in nasal sprays.

XXXXX

- Provided a detailed background on the use of cough and cold medicines in Australia.
- Noted that although there was significant demand for these products for all age groups, paediatric preparations were particularly popular because of parents' natural concern for their children and a desire to provide treatment when available. The conditions were usually self-limiting and not serious in nature and capable of self-

management for adults, or management by a parent or guardian for children, particularly with access to health professional support (i.e. from a community pharmacist).

- The current proposed rescheduling addressed public safety issues and did so in a manner that maintained and promoted responsible public access to these medicines, particularly for children 2 to 6 years of age. There was an additional benefit of not having the medical system clogged by patients with minor ailments that could be effectively and appropriately dealt with by pharmacists.
- Suggested that the proposed rescheduling be extended to also apply to ammonium chloride, bromhexine and guaiphenesin. Previous concerns were that some mucolytic/expectorants such as ammonium chloride, bromhexine and guaiphenesin may have unintentionally been made Schedule 4. This was not now an issue. Including these substances under the current proposal would:
  - reduce confusion within the pharmacy setting regarding the storage and supply requirements for different products;
  - improve the safety aspect by facilitating access to health professional intervention and have little or no impact on public access; and
  - also be reasonable to expect this to be more manageable for industry.
- Noted and supported the exclusion of oxymetazoline and xylometazoline for 'nasal spray use', but argued that for greater flexibility it would be more appropriate to list the exclusion in more general terms, such as 'for topical nasal use'. This would ensure that other topical preparations (e.g. nasal drops) containing these substances would also be covered by the exclusion.
- Argued that products licensed for use in adults and children from 2 years of age but packaged and marketed as Schedule 2 products for use in adults and children over 6 years of age to include directions with the intent that 'use in children under 6 years of age should only be on the advice of a health professional'. This would prompt parents to seek accurate dosing advice from their pharmacist or doctor.
- Although not specifically scheduling matters, would also like to see as part of the product registration/licensing requirements, that metric measures are mandated for inclusion in all oral liquid preparations, and that paediatric dose instructions were listed by weight.

Previous concerns addressed

- Reiterated that it was opposed to the original TGA proposal to reschedule cough and cold medicines for use in children 2 to 6 years of age to Schedule 4 due to concern that, rather than improving the safety profile of these medicines, such a move may increase the risk of misadventure in this vulnerable paediatric group.
- Revisited their previous arguments regarding off-label use, significant impact on public access, additional financial burden etc.

- Noted that when these products were either Schedule 2 or Schedule 3, consumers would have access to counselling and advice from a highly trained health professional. This was particularly important for the parents or carers of young children. Acknowledging that as the risk was greater in children under 6 years of age, the decision for listing cough and cold medicines for use in children 2 to 6 years of age as Schedule 3 medicines was both practical and sensible.
- Summarised their previous concerns with the original TGA proposal regarding the effect on community pharmacy, such as confusion, capacity to manage the increase in Schedule 3 medicines etc.
- Noted that although the current proposed schedule change would have some impact on labelling, supply and storage requirements as well as on pharmacy capacity, it was much more manageable for both pharmacy and industry than the original TGA proposal.
- Summarised their previous concerns with the original TGA proposal regarding the effect on medical practice, such as lack of doctor familiarity with current cough and cold medicines, risk of incorrect dosing, pressure to prescribe, access to doctors, cost etc. It was noted that the current proposal addressed these concerns whilst facilitating access to pharmacist intervention. Pharmacists were well placed and experienced in assessing cough and cold symptoms, referring patients that require or would benefit from medical intervention.

Efficacy

- Argued that product efficacy was imperative to justify supply within Australia, but asserted that efficacy was a registration/licensing issue and not a scheduling issue. There has been little effective evaluation done on the efficacy of cough and cold medicines and many of the trials have not been well designed or have been too small in nature to be of use.
- Stated that although the general consensus was that the evidence to date was not sufficiently compelling to demonstrate the safety or efficacy of cough and cold medicines for any age group, a lack of evidence did not equate to evidence of lack of efficacy.

XXXXX

- Reiterated XXXXX arguments for limiting the proposed Schedule 2 restrictions to "up to 12 years of age" stating that the rescheduling for adults or children 12 years of age or over was outside the scope of the TGA Panel's review and reiterated XXXXX arguments that this was not in line with previous phenylephrine scheduling decisions.
- Reiterated the above arguments regarding the low number of reported ADR's. While acknowledging the concerns that there was a lack of robust efficacy data for some actives, argued that the Australian evidence did not support that there was a risk and that there was no clear evidence of a risk outweighing a benefit. Specifically, the

risk/benefit balance of phenylephrine did not warrant more restrictive scheduling in those over 12 years of age.

XXXXX

- Noted that capturing use in children 6 years of age in Schedule 2 rather than Schedule 3 would align with the regulatory actions in similar jurisdictions, such as the UK and NZ.

XXXXX

- Asserted that capturing use in adults and children over 6 years of age in Schedule 2 restricted access to the substances to a retail pharmacy setting only, greatly reducing overall access for symptomatic relief of cough and colds and increasing the burden on pharmacies. The risk/benefit ratio for many of these products would not appear to warrant any scheduling change for adults and reiterated the above arguments that the TGA Panel's review did not address efficacy in adults and children 12 years of age and over.
- The proposed Schedule 2 change also did not address the changing attitude of consumers that increasingly rely on the convenience of non–pharmacy retail when choosing symptomatic relief for self limiting conditions. These changes may cause switching in-store to the use of complementary medicines which have lower levels of evidence requirements and unknown safety profiles. Stated that this was not in-line with the intent of the original review.
- Sought to ensure that use of carbetapentane in adults and children 12 years of age and over was not captured by the Schedule 2 proposal XXXXX and provided some carbetapentane specific arguments including the following:
  - Unscheduled carbetapentane products have a long history of use. XXXXX.
  - The adverse events were all non-serious and demonstrated an excellent safety profile for the product.
  - Restriction of carbetapentane to Schedule 2 for use in children 6 years of age and over was not warranted. Any risk to children under 6 years of age could be adequately addressed by an age restriction on labelling without impeding access for use in children over 6 years of age for which no safety risk had been demonstrated.
  - Lack of efficacy data had been brought into question for this ingredient; however the historical use pattern and lack of any known serious safety risk to adults would indicate upscheduling to be unnecessary.
- Sought a similar consideration for phenylephrine XXXXX and provided specific arguments in relation to phenylephrine, including the following.
  - Unscheduled phenylephrine products have a long history of use. XXXXX.

- These specific products were not indicated for use in children 12 years of age or under.
- The adverse event profile predominantly referred to non-efficacy, however while this could be due to a rebound effect, product labels did have a warning to avoid prolonged use. There was no indication from this data that these products in their current format posed a known safety risk to adults.
- The products' safety profile was further enhanced by little to no risk of overdose if inadvertently taken by children due to the small container size XXXXX, presentations XXXXX, and low level of active XXXXX.
- Any rescheduling of this product would be unwarranted based on the evidence currently available.

XXXXX

- In supporting the Schedule 3 and 4 rescheduling proposal, reiterated XXXXX position that a more restrictive scheduling for use in children 2 to 6 years of age (i.e. TGA Panel's Schedule 4 recommendation) would most likely result in increased accidental overdose and inappropriate off-label use. Having the pharmacist involved in the dispensing of these medicines was likely to ensure safe and proper use and dosage of these medicines.
- Regarding the Schedule 2 rescheduling proposal, reiterated XXXXX argument that this inadvertently captures solid dose phenylephrine / phenylephrine combination products that were only recently reviewed by the NDPSC.

DECEMBER 2010 EXPERT ADVISORY COMMITTEE DISCUSSION

Members noted the process undertaken in determining the NDPSC's proposed rescheduling cascade and the supporting evidence. A Member asserted that the TGA undertook an exhaustive process in reaching their recommendations. These were then examined closely by the NDPSC and open to an extensive consultation process. Additional public consultation occurred prior to the December 2010 ACMS meeting. A Member asserted that no new studies on cough and cold preparations for children had been released, although it was noted that some Cochrane reviews had been withdrawn as the authors had been unable to update them due to time constraints. The Committee generally agreed with the majority of the NDPSC's June 2010 conclusions. A number of issues, however, warranted detailed re-examination in light of arguments presented in pre-meeting submissions.

Children 6 years of age and over

Members discussed the delegate's proposed cascade in relation to rescheduling of cough and cold preparations for use in children under 2 years of age to Schedule 4 and for use in children from 2 to 6 years of age to Schedule 3. Members reiterated many of the issues previously raised at the June 2010 NDPSC meeting, specifically noting the safety risks

and lack of efficacy of cough and cold preparations for children. One Member asserted that the proposed rescheduling raised a significant risk of off-label use in children. However, several other Members asserted that such a risk was present in many rescheduling decisions and should not preclude a decision on this matter. Members also noted the role of the pharmacist in providing advice to consumers as well as appropriate labelling requirements and asserted these would provide a guide to inform parents on the appropriate use of these medicines.

A Member verbally advised the meeting that the NSW PIC had provided childhood poisoning data to the TGA in March 2010. It was noted that from 2004 to 2009, there were over 11,000 reports to the PIC of unintentional ingestions of cough and cold preparations by children under 5 years of age, of which 8 to 13 per cent were referred to hospital. Members noted that while this data was not previously available to inform the TGA recommendations (which were based on overseas poisoning statistics), it supported the current proposal under consideration.

It was noted that the majority of pre-meeting submissions supported the proposed rescheduling for use in children under 2 years of age to Schedule 4 and for use in children from 2 to 6 years of age (inclusive) to Schedule 3. One pre-meeting submission requested that the Schedule 3 proposal not include use in children 6 years of age (who would then be captured by Schedule 2), however, this was not supported by the Committee. Members agreed that the NDPSC proposed rescheduling cascade for children under 2 years of age and for children from 2 to 6 years of age (inclusive) was appropriate.

Adults and children over 6 years of age

The Committee discussed the appropriateness of the rescheduling of cough and cold preparations for use in adults and children over 6 years of age to Schedule 2, as raised in several submissions. Members noted the request for the proposed cascade not to apply to cough and cold preparations for use in adults and children over 12 years of age (Schedule 2 for use in children over 6 years of age to 12 years of age only). A Member asserted that this proposal was not appropriate as the benefits associated with these preparations for use in adults and children over 12 years of age did not outweigh the risks, particularly noting the lack of evidence of efficacy and that these products were only used for symptomatic relief. The Member further argued that the fact that these products were widely used in view of the lack of efficacy was a good indicator of the need for a Schedule 2 restriction for adults and children over 6 years of age. Another Member also noted that access to these preparations would still be available from pharmacies and consumers would have the opportunity to obtain pharmacist advice on alternative preparations and more appropriate treatments.

A Member expressed his concern at the principle of placing medicines in Schedule 4 when toxicity data were minimal. To create a criminal offence on the part of the supplier and the receiver (in some jurisdictions) could be a disproportionate response. The Member also observed that restricting a medicine to Schedule 4, and therefore limiting its

supply to medical prescription, should not imply its efficacy. For these reasons, the Member argued that the matter could be more appropriately addressed through the registration system (including labelling) insisting that the lack of efficacy was an issue of great importance.

A Member asserted that although labelling and registration does serve to ensure appropriate use of medicines, the rescheduling of cough and cold preparations for both adults and children would send a definitive message in relation to these medicines' risks and efficacy. A Member also reiterated that the pre-meeting submissions reflected a general sense of acceptance of the proposed cascade, with minor variations. Members generally agreed that the NDPSC proposed rescheduling cascade appropriately balanced the risks and benefits of cough and cold preparations for adults and children.

Exceptions

Members generally agreed with the NDPSC's previous decision that bromhexine, guaiphenesin and ammonium salts should not be included in the current consideration. The reasons previously reiterated by the NDPSC for these exclusions (better risk profiles, efficacy, and harmonisation) were supported by ACMS Members. It was also noted that if the delegate wished to amend the scheduling of these substances, a new delegate's consideration would need to be commenced.

Members also noted the pre-meeting submissions on the NDPSC's exception wording for oxymetazoline and xylometazoline "for nasal spray use". A Member asserted and the Committee generally agreed that both nasal sprays and nasal drops, by their presentation, were unlikely to result in accidental poisoning. Members also noted that the TGA did not include nasal preparations in their recommendations. Members agreed that the wording "for nasal use" would more appropriately capture both types of presentations.

The Committee discussed the proposed rescheduling cascade in relation to phenylephrine preparations for adults and children 12 years of age and over. It was noted that the NDPSC recently considered the scheduling of phenylephrine products, specifically combinations involving paracetamol, guaiphenesin and phenylephrine. A combination of paracetamol with phenylephrine plus or minus guaiphenesin is currently unscheduled, provided it is not labelled for use in children under 12 years of age. Members generally agreed that the proposed rescheduling should not apply to those phenylephrine cough and cold preparations which are currently unscheduled, i.e. for use in adults and children aged 12 years of age and over.

Members also discussed the proposed rescheduling cascade in relation to carbetapentane preparations for adults and children 12 years of age and over. A Member argued that there was no evidence of greater efficacy of carbetapentane cough and cold preparations over other preparations. However, another Member asserted that carbetapentane was currently classified as a Listed Ingredient by the TGA and had been appropriately assessed as such. Members also noted the long history of the unscheduled use of low concentrations of carbetapentane. Members generally agreed that the proposed

rescheduling should not apply to carbetapentane in cough and cold preparations for use in adults and children 12 years of age and over.

Members discussed the proposed scheduling in relation to senega in cough and cold preparations for all ages. A Member asserted that any risk of accidental poisoning in children was largely mitigated due to the taste of senega. Another Member also noted the long history of the availability of unscheduled senega in combination with ammonia. The Committee agreed that senega should be excluded from the proposed scheduling cascade and remain unscheduled.

Other matters

A Member noted that currently there was a Schedule 2 cough and cold entry for trimeprazine. Trimeprazine was neither a part of this, nor NDPSC's June 2010 consideration and was not included in the delegate's proposal. The Committee noted that this may be due to the fact that there did not appear to be any combination cough and cold products containing trimeprazine currently available and agreed that this issue may not require action at this time.

Implementation date

A Member asserted that due to the yearly cycle in seasonal demand for cough and cold preparations the timing of any decision would need to be considered closely. Members agreed that a long implementation time for the proposed rescheduling could be allowed for labelling changes, etc.

A Member suggested an implementation time of 12 to 18 months following the delegate's final decision, i.e. not prior to the 2012 cough and cold season. Other Members suggested that in this instance, a specific implementation date should be recommended to the delegate. Members agreed that an implementation date of 1 May 2012 would be appropriate (SUSMP No. 2 Amendment 3).

JUNE 2011 ACMS CONSIDERATION

DELEGATE'S REFERRAL TO JUNE 2011 EXPERT ADVISORY COMMITTEE

Cough and Cold preparations: Following consideration of advice from a number of expert sources including the Advisory Committee on Medicines Scheduling (ACMS), the delegate refers the following revised proposal regarding cough and cold preparations to the ACMS for further advice:

Cough and cold preparations – proposal to schedule five substances used in currently unscheduled cough and cold preparations to Schedule 2. The delegate proposes that this rescheduling apply to the following substances for use in cough and cold products only where it will not result in less restrictive scheduling:

· Carbetapentane (pentoxyverine)

- Guaiphenesin (guaifenesin)
- Ipecacuanha (cephaelis acuminata and cephaelis ipecacuanha)
- Phenylephrine
- Senega

The TGA proposes to address the use of cough and cold medicines by different age groups separately through product registration and labelling processes.

Additional information for stakeholders on the TGA review of cough and cold medicines is available at www.tga.gov.au/npmeds/consult/drlp-ccmedicines.htm. [**Note**: The web address has since changed to www.tga.gov.au/pdf/consult/consult-labelling-cough-cold-091022-review.pdf].

JUNE 2011 EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the scheduling of carbetapentane, guaiphenesin, ipecacuanha, phenylephrine and senega remain unchanged.

JUNE 2011 SUBMISSIONS

Further TGA advice

The TGA advised that it had reconsidered its earlier suggestions to the NDPSC and the ACMS regarding the scheduling of cough and cold preparations. The TGA asserted that the December 2010 ACMS recommendation, while largely reflecting the original TGA intent, was overly complex for sponsors, pharmacists and consumers and would be inconsistent with recent TGA regulatory actions resulting from the Review.

The TGA's revised recommendation was to suggest reconsideration of the scheduling of the following five substances when used as active ingredients in OTC cough and cold medicines which, the TGA argued, would better reflect the outcomes of the Review and help achieve the desired restrictions on the use of these medicines in children:

Substance	TGA proposed change under consideration
Carbetapentane	Schedule 2 for any concentration.
Guaiphenesin	Schedule 2 for all current Schedule 2 and unscheduled preparations.
Ipecacuanha	Schedule 2 for unscheduled preparations indicated for coughs and colds.
Phenylephrine	From unscheduled to Schedule 2 when indicated for coughs and colds.
Senega	Schedule 2 at any concentration when indicated for coughs and colds.

The TGA recommended no change to the current scheduling of the following substances when used as active ingredients in OTC cough and cold medicines:

- Codeine, dihydrocodeine, bromhexine, dextromethorphan, pholcodine, pseudoephedrine, oxymetazoline and xylometazoline.
- The antihistamines brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine and triprolidine to remain unchanged (currently Schedule 4 for use in children under 2 years – use for treatment of coughs and colds could be addressed through labelling).
- Ammonium salts to remain unscheduled.

The TGA provided information on regulatory actions for cough and cold preparations currently underway, noting that packaging, labelling and scheduling were intended to work as a "package" to reduce or eliminate inappropriate use and harm:

- Measures to ensure that all OTC cough and cold medicines were in child-resistant packaging (CRP) to reduce the risk of accidental self-poisoning of young children. Almost all cough and cold medicines were already in CRP (even where they do not contain drugs currently required to have such packaging), however, such a requirement was being formalised to ensure compliance for future products.
- Inclusion of a mandatory warning on the label not to use these medicines for the treatment of coughs and colds in children aged less than 6 years to reduce the risk of parents and caregivers causing harm by administering these medicines to that age group. In some instances, this warning may extend to children up to 12 years (at the sponsor's discretion). These warnings would be included regardless of scheduling.
- Inclusion of a label warning that the medicine should only be used in children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner to reduce inappropriate use. Having the dosages for that age group on the label would enable parents and caregivers to administer a safe dose rather than guess.

Noted that as at mid-January 2011, there were over 570 registered OTC cough and cold products on the ARTG. Of these only 15 products (all liquid) did not contain at least one scheduled drug and could therefore be marketed through general retail outlets. A recent search of the ARTG revealed the following unscheduled products:

Substance	Registered products	Listed products
Carbetapentane	1 unscheduled cough and cold product. 0 non-cough and cold products.	0 products
Guaiphenesin	3 unscheduled cough and cold products 0 non-cough and cold products.	0 products.
Ipecacuanha	2 unscheduled cough and cold products. 2 unscheduled non-cough and cold products.	6 cough and cold and 5 non-cough and cold products.
Phenylephrine	Numerous unscheduled products both for cough and cold and other indications.	0 products.
Senega	10 unscheduled products (with or without ammonia).	6 cough and cold and 8 non-cough and cold

products.

In the TGA's view:

- None of the cough and cold medicines containing the drug substances considered in the Review (other than ammonium salts) should be unscheduled. They should only be available through pharmacies where appropriate advice would be available, if required. This advice may be needed for use of these products in adults as well as children.
- Scheduling of cough and cold medicines based on the age of the intended recipient would be confusing and impractical as:
  - pharmacy-only medicines were routinely purchased with the transaction being handled by a pharmacy assistant without the customer having any discussion with a pharmacist;
  - pharmacists were unlikely to want to be involved in more than a small proportion of sales of these medicines;
  - the purchaser was under no compulsion to reveal the age of the person for whom the product was intended; and
  - a product may have been purchased for one household member and then be used for others.
- Making these medicines at least Schedule 2 for all ages and relying on the labelling to alert the consumer to appropriate use in children would be simpler, less confusing and still achieve the desired outcome of the Review.

June 2011 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX.

XXXXX opposed the revised proposal in general (however most XXXXX comments were restricted to guaiphenesin and phenylephrine). XXXXX objected to the proposal in relation to guaiphenesin and phenylephrine, however did not object to the proposal regarding the remaining 3 substances. XXXXX opposed the scheduling specifically in relation to guaiphenesin but did not comment on the other four substances. XXXXX supported the revised proposal.

One late submission was received from XXXXX opposing the proposed rescheduling.

Several submissions requested publication of the reasons for the revised proposal and clarification of the status of the remaining 15 cough and cold substances previously included in the December 2010 ACMS consideration. Members noted, as mentioned above, that the minutes from the December 2010 meeting as well as edited pre-meeting submissions would be published once an interim decision was made on this matter.

XXXXX did not provide further comment apart from indicating its position, however, other pre-meeting submissions also made a number of points, as summarised below (apart from XXXXX submission, which only reiterated points already made by other pre-meeting submissions):

XXXXX – guaiphenesin & phenylephrine

- Contended that the existing scheduling arrangements were appropriate. Some restrictions based on age could be made to the existing scheduling to satisfy safety issues in use in children. Suggested an age-based exemption from Schedule 2 for guaiphenesin and phenylephrine when present as sole actives for use in adults and children over 12 years (similar to the existing exemptions for these actives when combined with paracetamol).
- Noted that the TGA Review focussed on safety in children, predominantly those under 6 years of age. Stated that phenylephrine and guaiphenesin in combination with paracetamol were unscheduled only in small packs when indicated for children over 12 years and adults. Asserted that it was unclear how scheduling of these products would affect safety in children, since these products were not used by children.
- Stated that other countries such as the UK, USA, New Zealand and Canada had not tightened the restrictions on products indicated for adults and children over 12 years of age, particularly those products that have adult dosage forms (e.g. tablets and capsules).
- Noted that "cold and flu" were allowable indications for paracetamol and ibuprofen products, some of which were unscheduled and marketed in the grocery environment under brand names that include the words "cold & flu". Raised concerns that potentially the only unscheduled products that could be marketed with a cold and flu indication would contain analgesics only. Asserted that this would imply that paracetamol had a better safety profile than phenylephrine and guaiphenesin, which was not the case.
- Noted the February 2010 NDPSC decision to exempt guaiphenesin when combined with paracetamol for adults and children over 12 years. Asserted that the NDPSC agreed that the safety profile of these substances when combined indicated that their availability as unscheduled carried little risk. Stated that there was no rationale available to explain why this decision was no longer appropriate.
- Asserted that their proposed age based scheduling was preferable as it affected only the products that were labelled for use in children (i.e. its impact would be restricted to the population directly identified in the reviews commissioned by the TGA). Noted existing entries in the SUSMP which utilise this approach and still allow for the TGA to ensure appropriate use in children via labelling and registration.

- Requested harmonisation with NZ, stating that the majority of supplied formulations were trans-Tasman and harmonisation of labelling and packaging would help control costs to sponsors.
- Noted that the UK implemented new age-based classifications in March 2010:
  - Phenylephrine as general sale (GSL) i.e. unscheduled, for use by adults and children over 12 years. Maximum dose equivalent to 10 mg phenylephrine.
  - Guaiphenesin as GSL for adults and children over 12 years. Maximum dose 200 mg.

  Members also noted that in the UK, ipecacuanha is GSL for use by adults and children over 12 years. All senega preparations are also available as GSL.
- Noted that in Canada guaiphenesin was GSL, and phenylephrine was GSL when in low concentrations. Use in children was managed mainly via labelling.
- Stated that changes to scheduling would result in changes to labelling as well as variations for consideration by the TGA. Requested consideration of 2013 as an implementation timeframe.

XXXXX – guaiphenesin and phenylephrine

- Asserted that there was no new data to suggest safety concerns surrounding guaiphenesin and phenylephrine, noting that these compounds were initially reviewed by the TGA and subsequently by the NDPSC and ACMS. Asserted that there had been no increased risk to public health or history of abuse for products containing these compounds.
- Requested that the recommendations made at the December 2010 ACMS meeting be adopted.
- Also commented on the scope of the TGA Review and its applicability to adults and children over 12 years of age.
- Stated that the revised proposal was inconsistent with the decisions made by regulators in other countries that effectively reviewed the same data. Stated that the proposed rescheduling would mean that only complementary products would be available through non-pharmacy retailers. Queried whether this would be in the interest of public health.
- Noted that the US was undertaking studies of 8 cough and cold substances representing about 95 per cent of the cough and cold paediatric market. These were expected to be completed in 2012-2013. Recommended that the information from these studies be considered in Australia when they become available before any further restrictions on cough and cold medicines were imposed.

(a) Risks and benefits

- Noted the long-term use of cough and cold products in Australia. Reiterated points from the TGA Review regarding poisonings data and the low rates of death or serious injury from children's cough and cold medicines.
- Conducted a literature review relating to the safety of cough and cold products from the period when TGA conducted the review of paediatric cough and cold medicines in 2009. Stated that no relevant publications were identified.
- Also noted the recent NDPSC considerations of phenylephrine and guaiphenesin when in combination with paracetamol and the resulting decisions to allow unscheduled access to specific presentations.

(b) Purpose and extent of use

- Stated that guaiphenesin is an expectorant and the ARTG listed 58 registered products with guaiphenesin as the active ingredient.
- Stated that phenylephrine is a nasal decongestant and the ARTG listed 231 registered products with phenylephrine as the active ingredient. Noted that as phenylephrine also had uses other than for nasal decongestion, this figure may not accurately represent cough and cold products.
- Noted that some products containing these active ingredients were unscheduled.

(c) Toxicity

- Noted points from a report prepared during an external independent review of paediatric cough and cold medicines [Members noted that the report was uncited and it was unclear which review the submission was referring to]:
  - These medicines were unlikely to be harmful in label dosages. Serious poisoning was rarely seen in non-intentional overdose in the typical 1-2 year old age group.
  - A recent US study demonstrated that OTC cough and cold preparations were present in toxicology screens in 5 per cent of life-threatening poisonings in children.
  - This may not apply to some drugs in adult doses in solid form, but this was not going to be influenced by any changes that might be made in the nature or availability of cough and cold medicines for children.
  - Overseas reports of serious poisoning including deaths from cough and cold medicines were generally not reflected in current Australian experience. Documentation of such deaths was often confounded by co-existing severe illness, multiple drug administration, solid drug forms, the possibility of homicide and other factors.
- Reiterated points from the TGA Review noting the adverse drug reaction rates (ADRs) for children. Stated that of the 14 serious ADRs reported between 1981-2010, phenylephrine was linked to one serious ADR (in a combination product

where causality could not be determined) and no serious ADRs were reported for guaiphenesin.

- Noted that a number of substances with different safety profiles (e.g. analgesics) were available to consumers as unscheduled medicines in non-pharmacy outlets. Asserted that the five substances in the revised proposal had favourable safety profiles when compared with some unscheduled substances.

(d) Labelling

- Noted the TGA labelling approval processes.

(e) Potential for abuse

- Asserted that there was no evidence in the Australian market suggesting patterns of misuse, either intentional or accidental. Stated that those products with abuse potential were already restricted to pharmacies.
- Stated that by making cough and cold products unavailable to children under 6 years of age, there would be an increased risk that carers would "guess" the dose for a child under 6, based on the dosage instructions on a package for children older than 6 years of age. Stated that this trend had been observed in the USA.
    - Members noted that this point appeared to relate to the lack of products registered for children under 6 years of age. Members noted that it was unclear how this point related to the current scheduling proposal which did not include age-based restrictions.

XXXXX

- Asserted that as the TGA would be managing issues surrounding appropriate use by age groups, the current scheduling of the five substances ought to be maintained to enable adult access to simple cough and cold medicines.
- Stated that the potential safety concerns of cough and cold medicines in general related to use in children where a lack of strong efficacy data was accompanied by some increased risks, in particular in cases where the recommended use and dosage had not been followed.
- Reiterated comments detailed above regarding the scope of the TGA Review and its applicability to adults and children over 12 years of age; inconsistency with decisions made by overseas regulators for cough and cold preparations; recent considerations of phenylephrine and guaiphenesin when combined with paracetamol; harmonisation with NZ scheduling; lack of new data available to support the revised proposal; comparison of safety profiles of currently unscheduled substances (e.g. analgesics); TGA labelling processes; and lack of evidence of misuse.
- Also reiterated points made earlier in relation to the TGA review and reported ADRs for phenylephrine and guaiphenesin. Noted that no serious ADRs were reported for

pentoxyverine or senega and ammonia. Noted the current use of child-resistant packaging for these products.

- Noted the regulatory effects of the proposed scheduling on senega which was classified by TGA as "Listed".
- Noted the scheduling of the five substances in NZ and in the UK from 1 March 2010 (detailed above).
- Provided a list of currently available XXXXX products that would be affected by the proposed rescheduling. Stated that there were several products containing paracetamol and/or phenylephrine and/or guaiphenesin either in the process of being evaluated by the TGA or had been approved which would be affected.
- Asserted that the potential regulatory impact of the proposed rescheduling was of such a magnitude that a full Regulatory Impact Statement (RIS) would need to be conducted to satisfy current Government policy guidelines. Asserted that evidence of gross market failure was required to justify the scale of the impact on consumer access, industry generally and sponsors specifically.
    - Members noted that due to the nature of scheduling decisions a RIS was not conducted. Scheduling decisions are made based on the protection of public health. Although potential regulatory impact may be a consideration for the implementation date of any changes, this was not a matter under section 52E of the Act that the decision-maker must take into account when considering scheduling.
- Requested a minimum of 9 months lead time to implement any changes arising from consideration of this matter. Suggested that the 2013 cough/cold season may be appropriate.

XXXXX – guaiphenesin

- Asserted that as most coughs were self-limiting, and given the low safety risk and efficacy to help relieve chesty cough, guaiphenesin scheduling should remain unchanged. Noted the long history of use of guaiphenesin in Australia and the previous NDPSC consideration of guaiphenesin+paracetamol combinations. Claimed that no new data had been presented to warrant additional restrictions.
- Noted that in April 2010, the MCC recommended retaining guaiphenesin as unscheduled following extensive review of data and evidence.
- Stated that the presentation of cough and cold medicines in Australia was more stringent than overseas, reducing risk of overdose or misuse.
- Asserted that of the 22 cough and cold substances in the TGA Review, guaiphenesin had the best benefit to risk profile. Stated that there was little reported risk from use of guaiphenesin in children aged 6 years and above.
- Requested a lead time of 18 months due to sourcing of products from overseas.

XXXXX – all

- Reiterated XXXXX position that the existing scheduling arrangements were appropriate, however some restrictions based on age could be made to satisfy safety issues in use in children.
- Also reiterated points made earlier in relation to the scope of the TGA review; reported ADRs for the five substances under consideration; the use of child-resistant packaging to mitigate risk; recent considerations of phenylephrine and guaiphenesin when combined with paracetamol; and inconsistency with decisions made by overseas regulators for cough and cold preparations.
- Stated that analysis of the safety data from Australia, New Zealand the UK, USA and Canada all showed that the actives responsible for most reports of adverse events were the sedating antihistamines and pseudoephedrine; these were already Schedule 2 or higher. Asserted that accidental childhood ingestion, followed by overdose, presented the highest risk factors for Australia.
- Asserted that the restricted availability of cough and cold medicines via pharmacy (antihistamines and pseudoephedrine) did not provide an effective solution for this problem as the events occur after purchase and in the home. Contended that up scheduling any other actives would seem to be of little benefit in preventing ADRs given it had not stopped events with medicines that were already Pharmacy Only.
- Stated that in 2009 the MCC did a similar review of cough and cold preparations. The MCC recommended that the scheduling of these preparations should remain unchanged and that cough/cold labels in New Zealand must also include a warning to "seek advice from a healthcare professional if taking more than one cough/cold medicine".
- Raised concerns regarding the regulatory impact of the proposed rescheduling. Asserted that a Schedule 2 classification would affect availability in rural areas. Stated that this was also against the Government's Self Care initiative and would further increase the burden on pharmacists and the health care system.

XXXXX – all

(a) Risks and benefits

- Asserted that products containing carbetapentane, guaiphenesin and phenylephrine posed little to no risk, with a safety profile exceeding that of many other unscheduled substances.
- Noted the long history of general sale availability of these products and stated that this was an indicator of benefit to consumers. Stated that the symptoms of cough and cold were easily identifiable and choice of symptomatic relief containing these actives did not require pharmacist intervention. Asserted that the risk benefit balance remained unchanged for these products and did not warrant any change to the current scheduling requirements.

(b) Purpose and extent of use

- Noted that XXXXX products affected by this review had an extensive pattern of use with approximately XXXXX units sold almost exclusively through the grocery (unscheduled) channel. Asserted that this was an indication of the degree of access to symptomatic relief for mild and self limiting conditions that these products and the grocery channel provide.
- Stated that although the products were not marketed to paediatric populations, they did have in some cases dose ranges for children under 12. Asserted that the products met a community need for ease of access to effective medicines for the relief of symptoms in self limiting conditions. Stated that this need would remain unchanged due to the changing purchasing habits of the consumer and would ultimately be met by complementary medicines should the proposed scheduling change occur.

(c) Toxicity

- Asserted that the toxicity profile of the products did not warrant any change in scheduling and was better than other active ingredients which were currently unscheduled.
- Reiterated points made earlier in relation to the ADRs for the five substances under consideration reported in the TGA Review. Stated that they have received no serious ADRs for any products containing the five substances in the revised proposal.
- Stated that products containing the five actives the subject of this proposal were all contained in child resistant packaging.

(d) Labelling

- Stated that concerns regarding use in paediatric populations could be adequately addressed by age related labelling rather than by rescheduling to a pharmacy only setting.

(e) Potential for abuse

- Was unaware of any abuse/misuse of products containing these substances, either intentional or accidental. Asserted that a scheduling change would have no impact on this potential and would only serve to reduce availability to the adult population.

XXXXX – all

- Noted that a number of popular unscheduled cold and cough syrups would be affected by the proposed rescheduling. Stated that these products had a long history of unscheduled access with little evidence of misuse.
- Stated that unscheduled access resulted in lower prices, longer hours of access (especially in regional communities) and shorter distances of travel for access. Stated that potential risks could be adequately addressed via means other than scheduling (e.g. labelling) without unintended consequences for consumers.

XXXXX (a pharmacist) – all

- Asserted that the substances under consideration were safe and effective and current restrictions were appropriate, allowing for inexpensive access. Asserted that consumers could appropriately self-select these cough and cold preparations and that the proposed rescheduling would constitute over-regulation.

XXXXX – all

- Asserted that some of the cough and cold products which had been available for a long time had indications which were accepted following lower levels of evidence than what was now required. Asserted that these products had not previously been required to demonstrate their efficacy for registration on the ARTG due to their 'grandfathering' onto the register.
- The inclusion of warnings and directions on packs did not surmount the issues associated with poor consumer health literacy without the opportunity for counselling.
- Access through the pharmacy sector was more than adequate and provided access to health professional advice to support quality use of medicines objectives.

(a) Risk and benefits

- Noted that paracetamol was one of the most frequently used drugs in Australia and was used in many forms either alone or in combination with other drugs. Raised concerns in relation to combination cough and cold products containing paracetamol and the risk of accidental paracetamol overdose due to inadvertent dose duplication.
  - Members noted that the only unscheduled paracetamol combinations were products containing phenylephrine, guaiphenesin, and/or effervescent agents.
- Stated that paracetamol was the most common means of drug overdose in the UK and it was not unreasonable to assume that it had a similar profile in Australia. Noted an Irish report observing that there was an increase in the proportion of intentional paracetamol overdoses in 1999 and that for accidental paracetamol poisoning, children under the age of 5 years accounted for approximately 20 per cent of admissions. This report identified that the incidence of paracetamol poisoning was related to its ease of access.
- Noted that nearly half of the paracetamol overdose cases in the USA were due to accidental overdose and reported the following as contributing factors:
  - Consumers attempting to treat different symptoms with multiple products containing paracetamol, not realising that paracetamol was an ingredient common to each.
  - The association between paracetamol and liver injury was not common knowledge.

- Extensive retail availability may contribute to the perception that the ingredient was unlikely to be harmful.

(b) Purpose and extent of use

· Noted that as the common cold was a self-limiting, non-life-threatening condition, the use of cough and cold preparations was limited to symptomatic relief. Asserted that at-risk populations would need to be identified with consideration given to: situations requiring referral; drug-disease interactions; and drug-drug interactions.

· Asserted that due to risks associated with misdiagnosis and product misuse, particular attention should be paid to drug usage and product choice in the young, elderly and those with renal and hepatic impairment.

(c) Toxicity

· Stated that phenylephrine may impact on the control of diabetes, heart disease, hypertension, prostatic hypertrophy, glaucoma and hyperthyroidism. It may also interact with monoamine oxidase inhibitors and other sympathomimetic drugs.

· Noted that phenylephrine is a Pregnancy Category B2 drug, indicating that there was limited data available as to its interactions in breast-feeding and pregnancy. Stated that it was excreted in breast milk, however absorption from the gastrointestinal tract was erratic. Stated that it is recommended to avoid the use of oral preparations when breast-feeding.

· Stated that drug-disease precautions for expectorants such as guaiphenesin, senega and ipecacuanha included hepatic impairment, renal impairment and gastrointestinal ulceration.

(d) Dosage, formulation, labelling

· Noted common assertions in exemption applications that risks could be mitigated through labelling. Raised concerns that people did not read labels, and if they did, often did not understand the content.

· Referred to an Australian Bureau of Statistics survey indicating that a number of Australians (including people whose language was not English) did not have sufficient literacy skills to meet the complex demands of everyday work and life, and that on the health scale, 60 per cent attained scores below the minimum requirement to meet everyday needs. Stated that in the interest of public safety, it was essential to aim support at people with limited health literacy.

(e) Potential for abuse / misuse

· Raised concerns that any medicine available as general sale may be inadvertently misused and there was a risk of administration to children or the elderly, or use for extended periods without consulting a health professional.

(f) Other matters

- Noted the wide distribution of pharmacies and increases in extended trading hours. Noted that country pharmacists also provide after-hours patient access for urgent cases. Stated that it was common for pharmacies in both rural and metropolitan areas to offer delivery services for local areas.
- Stated that in some jurisdictions, store trading hour regulations meant that after-hours pharmacy access may be as good as or better than that through the grocery sector.
- Asserted that people with cold symptoms presenting to a pharmacy also facilitated the opportunity to check on a person's immunisation status for influenza and pertussis. This can be useful when targeting at-risk population groups, particularly when attempting to address outbreaks as with the recent pertussis outbreak in many Australian jurisdictions.
- Noted that restricting access to the pharmacy sector provided opportunities to note 'red flags' for referral to the pharmacist, such as requests for multiple packs or repeat purchases, pregnancy, breast-feeding or people taking other medicines or presenting with other symptoms such as fever or asthma.
- Noted that pharmacists were able to advise consumers on effective and cost-effective therapies for the symptomatic relief of colds and flu.

Select history of previous NDPSC exemptions

Carbetapentane

In February 1977, carbetapentane was included in Schedule 2 with an exemption for preparations containing 0.5 per cent or less of carbetapentane (the current entry). In August 1985, deletion of this exemption was considered following toxicity concerns; however, this was not supported.

Guaiphenesin

In February 1998, the NDPSC agreed to exempt guaiphenesin in oral preparations when accompanied by a statement warning against use in children under two years of age. In May 2001, to harmonise with NZ the NDPSC decided to delete the Schedule 2 entry and amend the Schedule 4 entry to exempt divided preparations containing 200 mg or less of guaiphenesin and oral liquid preparations containing 2 per cent or less of guaiphenesin.

In February 2010, the NDPSC decided to extend the exemption for certain paracetamol+phenylephrine combination products to also include combinations containing guaiphenesin.

Ipecacuanha

In October 2006, as part of harmonisation with NZ, the NDPSC decided to include ipecacuanha (*Cepahelis acuminata* and *Cephaelis ipecacuanha*) in Schedule 4 with an exemption for preparations containing 0.2 per cent or less of emetine (the current entry).

Phenylephrine

In October 2005, the NDPSC considered harmonising with NZ on the scheduling of phenylephrine. The NDPSC decided to increase the exemption from scheduling for oral use to include preparations containing 50 mg or less per recommended daily dose.

In June 2007, the NDPSC decided to extend the exemption from the limit on paracetamol combinations being allowed as general sale products to include phenylephrine (as long as it also qualified as exempt from scheduling through the phenylephrine entries). At that time, the NDPSC considered that the safety profile of these substances was such that allowing a fixed combination to be unscheduled was reasonable.

Recent NZ MCC considerations

Ipecacuanha

In November 2010, the MCC confirmed their previous recommendation that ipecacuanha should be reclassified from general sale (unscheduled) medicine to Pharmacy-Only medicine (Schedule 2 equivalent) for the treatment of the symptoms of cough and cold in children aged 6-12 years.

The MCC, however, also recommended that a dosage limit should be included in the reclassification of ipecacuanha so products with an alkaloid content of less than 40 mcg per dose were excluded and remained general sale medicines.

The MCC agreed that the known risks of toxicity for ipecacuanha were dose related and the cut-off dose and pack size meant it would be extremely unlikely that toxicity would be seen with the product under consideration even if the whole pack was consumed.

Guaiphenesin

In November 2010, the MCC did not support a request to include guaiphenesin in modified release tablets containing 600 mg or 1200 mg of guaiphenesin in packs containing more than five but not more than 10 days supply, as a pharmacy-only medicine. However, the MCC stated that it would be willing to support a limited increase to the general sale availability of lower concentrations of guaiphenesin.

In April 2011, following further comments, the MCC recommended increasing the general sale classification for guaiphenesin from 5 to 10 days supply (in modified release form for oral use in medicines containing 2 per cent or less or 200 mg or less per dose form, with a maximum recommended daily dose of not more than 2.4 g). The MCC also

recommended retaining guaiphenesin labelling warning of the potential risk of developing kidney stones.

Paracetamol combined with phenylephrine and guaiphenesin

Also in November 2010, the MCC noted the NDPSC's decision to extend the exemption for certain paracetamol plus phenylephrine combination products to also include combinations containing guaiphenesin. As NZ already allowed for combinations of paracetamol as general sale medicines with other active ingredients classified as general sale no further action was recommended.

JUNE 2011 EXPERT ADVISORY COMMITTEE DISCUSSION

A Member reiterated that all these 5 substances [referred for consideration at the June 2011 ACMS meeting], as stand alone ingredients, had low toxicity with no significant reason to warrant a general Schedule 2 listing. Several Members asserted that restricting access to these substances to pharmacies for consistency with other actives in cough and cold preparations, while potentially attractive for simplicity, was not appropriate. A Member also noted that changing the unscheduled status of these substances would be more restrictive than the status of these substances overseas, including NZ.

A Member noted, however, that up-scheduling to Schedule 2 would allow a parent to have ready access to a pharmacist for advice regarding the label warnings. Other Members argued that the risks appeared to be insufficient to make this availability of a pharmacist a necessary requirement of supply. A Member was also concerned that up-scheduling could remove the differentiation of these products from a number of Schedule 2 alternatives which were not as safe. Up-scheduling the 5 substances could also inadvertently increase the use of less safe products (e.g. sedating antihistamines). The Member also noted a number of complementary products available through general sale which were associated with less efficacy and safety data than these 5 substances. Another Member, in response to a specific concern raised in one public submission, asserted that there appeared to be little or no evidence provided of a particular problem of duplicate dosing of paracetamol cough and cold preparations with other general sale paracetamol products.

Members noted that most of the identified risks were for children less than 6 years of age. The Members noted that the TGA was taking action to mitigate these risks (particularly labelling, such as contraindications for use in children below 6 years of age, and packaging, including a requirement that all cough and cold preparations be in child-resistant packaging). A Member also noted that cough and cold was a self limiting indication, asserting therefore that less weight should be given to potential risks that could arise from long term over-use.

One Member suggested, while not supporting Schedule 2 for the other 3 substances, that perhaps Schedule 2 entries for phenylephrine and guaiphenesin for children under 12

should be considered. Other Members asserted that this was unnecessary in light of the actions on labelling and registration being undertaken by the TGA, i.e. that phenylephrine and guaiphenesin products currently available as general sale were restricted for adult use only.

A Member noted that the fundamental need was for a change in general attitudes to treating cough and cold in children. This was more likely to be achieved through the TGA's labelling actions than by up scheduling. Members agreed that a public education campaign on this issue was needed to facilitate change.

Other matters – Appendix F

Members considered whether the Appendix F entry for phenylephrine in nasal preparations for topical use was still required. Labelling requirements for OTC medicines were regulated through the TGA's *Required Advisory Statements for Medicine Labels* (RASML). RASML currently listed requirements for phenylephrine in nasal preparations for topical use to be labelled with statements 76 (*If congestion persists, consult your doctor or pharmacist*) – i.e. consistent with the Appendix F warning statement. The only application of the Appendix F labelling would therefore be where a phenylephrine preparation was not regulated by the TGA (i.e. dispensed as a compounded preparation).

Members noted that while Appendix L was intended to have replaced Appendix F for setting out minimum labelling requirements for medicines not subject to RASML (i.e. dispensed as a compounded preparation), not all jurisdictions had as yet made this transition in their own legislation. Members agreed that as some jurisdictions still referenced the Appendix F entries it was not yet appropriate to delete human therapeutic substances, such as phenylephrine, from this appendix.

DELEGATE'S INTERIM DISCUSSION

The delegate noted the ACMS' December 2010 recommendations, TGA's further advice, the resulting ACMS recommendations from the June 2011 meeting and all valid submissions received on this matter.

In relation to the age-based cascade for the 19 cough and cold substances considered by the ACMS in December 2010, the delegate agreed that appropriate restrictions in use by specific age groups would be appropriately addressed through the TGA's labelling and registration processes.

In relation to the proposal regarding the five substances in cough and cold preparations currently available as unscheduled considered by the ACMS in June 2011, the delegate agreed that the recommendations from the ACMS were clear and appropriately supported. The delegate agreed that the scheduling of carbetapentane, guaiphenesin, ipecacuanha, phenylephrine and senega should remain unchanged and use by specific age

groups would be appropriately addressed through the TGA's labelling and registration processes.

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; (d) the dosage, formulation, labelling, packaging and presentation; and (e) the potential for abuse.

Administrative matters

The delegate noted that the usual practice was to incorporate the summary of the ACMS' discussion into the delegate's reasons for interim decision published on the TGA website – i.e. it was not envisaged that ACMS minutes would be separately published. As no interim decision was made following the December 2010 ACMS consideration of this matter neither the discussion, considered at that meeting were published.

The delegate also noted that for transparency, the record of the December 2010 ACMS meeting (including the discussion and submissions summary) would be published along with the records of the June 2011 ACMS consideration in the delegate's reasons for that interim decision.

Once the interim decision was published, those stakeholders who provided a pre-meeting submission would be invited to make further submissions. This invitation was expected to be extended both to stakeholders who made a pre-meeting submission to either the December 2010 and/or the June 2011 considerations of this matter.

DELEGATE'S INTERIM DECISION

The delegate decided that the scheduling of carbetapentane, guaiphenesin, ipecacuanha, phenylephrine and senega remained appropriate (i.e. no change to current scheduling). The delegate also decided that the scheduling of the following 15 substances in cough and cold preparations remained appropriate (i.e. no change to current scheduling):

Brompheniramine, chlorpheniramine, codeine, dexchlorpheniramine, dextromethorphan, dihydrocodeine, diphenhydramine, doxylamine, oxymetazoline, pheniramine, pholcodine, promethazine, pseudoephedrine, triprolidine and xylometazoline.

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate decided that the scheduling of carbetapentane, guaiphenesin, ipecacuanha, phenylephrine and senega remained appropriate (i.e. no change to current scheduling).

The delegate also decided that the scheduling of the following 15 substances in cough and cold preparations remained appropriate (i.e. no change to current scheduling):

Brompheniramine, chlorpheniramine, codeine, dexchlorpheniramine, dextromethorphan, dihydrocodeine, diphenhydramine, doxylamine, oxymetazoline, pheniramine, pholcodine, promethazine, pseudoephedrine, triprolidine and xylometazoline.

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

2.2.1 RABEPRAZOLE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Rabeprazole – proposal to create a new entry for rabeprazole 10 mg or less in Appendix H.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

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

BACKGROUND

Rabeprazole is a proton pump inhibitor (PPI) indicated for the treatment of peptic ulcer disease and gastro-oesophageal reflux disorder (GORD). PPIs suppress gastric acid secretion by inhibiting the hydrogen potassium ATPase irreversibly, blocking the final step in gastric acid secretion.

Rabeprazole was first included in Schedule 4 in November 2000.

In June 2009, the NDPSC decided to down schedule 10 mg or less of rabeprazole for the relief of heartburn and other GORD symptoms, in packs of up to 14 days supply, from Schedule 4 to Schedule 3. At that time the NDPSC rejected an associated request to list rabeprazole in Appendix H on the basis that an insufficient case had been mounted for the public benefit from advertising rabeprazole.

In February 2010, the NDPSC agreed to editorially amend the Schedule 3 rabeprazole entry for consistency with other PPIs by adding "per dosage unit".

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

XXXXX submitted an application in support of an Appendix H listing for rabeprazole 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 June 2011 ACMS meeting.

Other recent PPI Appendix H considerations

In February 2010, the NDPSC rejected an application for Appendix H listing of pantoprazole. At the same meeting, two other PPIs, lansoprazole and omeprazole, were included in Schedule 3 (similarly to the rabeprazole and pantoprazole scheduling) to harmonise with New Zealand (NZ). In both cases it was agreed that a consistent approach for all PPIs should be undertaken in relation to Appendix H listing (i.e. these substances were not listed in Appendix H).

In June 2011, a delegate published a final decision agreeing with the February 2011 ACMS recommendation to not support an application to list pantoprazole in Appendix H. Relevant points from this consideration are summarised in the "2011 Pantoprazole Considerations" section below.

SCHEDULING STATUS

Rabeprazole is in Schedule 4 with a cut-off to Schedule 3 for oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply. This is not harmonised with NZ, which has yet to consider a Schedule 3 entry.

INITIAL SUBMISSIONS

Applicant's Submission

XXXXX requested an Appendix H listing for rabeprazole. Members particularly noted the following (additional detailed discussion of points from the application are also set out in the 'Evaluation' section below):

- Asserted that, in Australia, there were a large number of consumers who experienced symptoms of GORD such as frequent heartburn and reflux symptoms. Prevalence studies and other research show that many of these people were either untreated or under-treating e.g. with antacids, which were not as effective as PPIs.
- Argued that Schedule 3 availability in itself did not equate to public or consumer awareness, and many reflux sufferers may be unaware that pharmacists can recommend a PPI for frequent heartburn associated with GORD.
- Some consumers were chronic users of antacids, which had very low efficacy, and H_2 receptor antagonists (H_2RAs). Many of these consumers would benefit from a course

of PPI treatment but were unaware of its availability. Increased consumer awareness of a more effective treatment would be beneficial to this group of consumers.

- Use of a short course of PPIs was cost effective and provided cost benefits and improvement to quality of life for GORD sufferers. Untreated GORD was a significant cause of absenteeism and treatment of GORD with on-demand rabeprazole has been found to improve patients' quality of life and psychological wellbeing.
- Argued that advertising of rabeprazole was expected to increase awareness of frequent heartburn and reflux as a condition that could be managed appropriately. Advertising would encourage consumers to seek the advice of a pharmacist or doctor as to whether rabeprazole was appropriate for them (in particular those whose symptoms were currently not being managed well with available OTC treatments). Screening by pharmacists would identify any patients with symptoms of serious disease that required referral or those who could benefit from use of Schedule 3 rabeprazole.
- Asserted that there was little risk to the community from advertising PPIs for symptomatic treatment of GORD. PPIs were available on prescription for many years and the safety profile was quite well known. OTC PPIs were available as 14 day treatment packs and due to the short length of treatment there was little risk that serious symptoms would be masked or that diagnosis of serious conditions will be delayed. Pharmacists would continue to have control of the product at the point of sale and would refer any patients with "alarm" symptoms. Pharmacists had guidelines for supply of PPIs and, due to the length of time that pantoprazole had been marketed, they were familiar with indications, contraindications and when to refer. The potential inappropriate use for non-GORD indications was very low.
- A Schedule 3 rabeprazole product was launched in early 2011. At the time of the application educational material for pharmacists was being prepared in collaboration with the Pharmaceutical Society of Australia (PSA), and pharmacy assistants were also to be provided with unbranded educational materials relating to GORD to assist them in referring patients to the pharmacist.
- Argued that the safety of PPIs as a group was equivalent to that of H_2RAs, which were unscheduled and able to be advertised freely.

Members also noted the following more general points from the application:

- Stated that rabeprazole and pantoprazole were both PPIs and could be considered to be equivalent in efficacy, though there may be some minor differences in pharmacokinetic profile and potency. Both were listed in Schedule 3. The applicant argued that both pantoprazole and rabeprazole should be viewed similarly in terms of Appendix H approval to advertise directly to the public. Members noted, as discussed below, that the evaluator was unclear on the specific intent of this point.
- Asserted that in Australia medical visits and prescription PPIs were subsidised, therefore there was a significant cost associated with continuation of use of OTC PPIs; this acted as a further deterrent for inappropriate use of OTC PPIs.

The application also included two expert opinions (XXXXX, although XXXXX opinion appears to be giving a broader opinion on PPIs in general on behalf of XXXXX). The documents did not disclose the relationship of these experts to the applicant (however, both of these experts supported, in pre-meeting submissions, the previous pantoprazole Appendix H application). These opinions presented a number of arguments, including:

XXXXX

- Claimed that a number of surveys had shown that more patients reported heartburn symptoms than were receiving effective therapy. Many heartburn suffers has symptoms occurring at a frequency associated with impairment of quality of life.
- PPIs were the most effective therapy for the management of oesophageal reflux as, in clinical trials, they were superior to alternative therapies. Appropriate awareness that PPIs were available OTC may therefore be of benefit.
- There was the potential for community benefit from easy access to a common and safe treatment for a common disorder.
- In Australia, PPIs had been readily available by prescription but were relatively new as OTC products, so there may be less public awareness of availability. Appropriately targeted education regarding the proper use of such agents may be beneficial.

XXXXX

- Advocated an approach that begins with simple therapy and progresses towards more complicated therapy and the need for awareness of this.
- Indicated that use of OTC PPIs may let pharmacists detect alarm symptoms which may not always trigger the patient to seek medical advice. Pharmacist consultation also allowed an opportunity to discuss lifestyle measures that might be important in long term management.
- There was little risk from OTC PPIs and significant benefit by having the opportunity to trigger a referral for further advice.

Evaluation Report

Recommendation

The evaluator recommended that the application not be approved as a consequence of the following:

- This evaluator was more inclined than the June 2010 evaluator to the view that the information submitted supported that advertising the availability of PPIs from pharmacies might deliver a public health benefit. The evaluator noted, however, that it was difficult to quantify this benefit.
- The application was deficient in the following which bear on the assessment of a public health benefit:

- Although some rather limited evidence was submitted that rabeprazole was as efficacious as other PPIs in treating GORD, the application included no reference to the adverse reactions profile of rabeprazole and whether or not it differed in any significant way from other PPIs;
- The application avoided mention of whether or not rabeprazole interacted with clopidogrel or prasugrel. That was surprising considering that this issue was highlighted by the previous evaluator as "a major drug safety concern of current interest which until disproven should preclude the advertising of any OTC PPI".
- It was also of concern, as http://clinicaltrials.gov listed a study titled "Influence of Rabeprazole on the Magnitude of the Antiplatelet Action of Clopidogrel" (Study NCT00989300). The importance of evidence specific to an individual PPI was emphasised by the reporting that pantoprazole did not interact with clopidogrel in the same way as omeprazole.
- It was also noted that the submitted packaging directed consumers to ask their doctor or pharmacist before use if taking digoxin or ketoconazole, but made no mention of clopidogrel.

Evaluator's discussion

The evaluator provided specific discussion of a number of matters, including:

Potential Public Health Benefits

· There were no quantitative data on public health benefits. The application again relied on the results of a Pharmacy audit in 2009. This states that 85/153 subjects who participated in an audit by pharmacists experienced frequent heartburn, defined as occurring on two or more days per week. This led the authors to claim that "*As PPIs are recognized as the most effective therapy for frequent heartburn, there is a potential to improve the management of heartburn by pharmacist intervention and recommendation of PPIs"*. While there was some merit in that proposition, the information in the paper did not permit an understanding of the extent to which the proposition held.

· The evaluator went on to summarise addition data from the audit. The evaluator also commented on the limitations of the audit results. In particular, the evaluator argued that the audits algorithm had not been validated in terms of examining a public health benefit.

Equivalence of rabeprazole and pantoprazole

· The application claimed that rabeprazole and pantoprazole "should be considered as a group in relation to Appendix H listing". The evaluator was unclear on the intent behind this statement, but possibly the applicant intended to argue that the longer OTC experience of pantoprazole should be applicable to rabeprazole.

- The evaluator discussed a 2003 meta-analysis cited by the applicant. The evaluator noted that, of the various papers the authors identified for the analysis, only two involved use of rabeprazole in GORD. Both compared rabeprazole 20 mg with omeprazole 20 mg. The meta-analysis only looked at efficacy, it did not consider safety.
- The application acknowledged that there were small differences in pharmacodynamic and pharmacokinetic parameters between various PPIs. The application gave no consideration to, and did not provide data about, the adverse events profile of rabeprazole versus other PPIs.
- The OTC presentation of rabeprazole had been approved by the TGA with the same labelling warnings as pantoprazole.
- The application did not include any reference to or data about whether or not rabeprazole had a clinically significant interaction with thienopyridines, even though the previous evaluator highlighted this as a major drug safety concern of current interest, which until disproven, should preclude the advertising of any OTC PPI.
- The evaluator noted that the CMI listed 5 medicines that may be affected by rabeprazole (digoxin, ketoconazole, clarithromycin, atazanavir and clopidogrel).

Increased consumer awareness

- The application quoted an unpublished 2002 survey which found that 42 per cent of respondents reported heartburn, with 22 per cent experiencing it at least once a month. The evaluator noted, however, that because of the age of the study, it was likely to be unreliable to extrapolate information about current treatments due to the increasing availability of PPIs and recent non-branded television advertising informing patients that a new treatment was available from their doctor.
- The application pointed to the possibility that many sufferers of GORD were aware of, and were purchasing, the advertised antacids and H_2RA medicines, while being unaware of the more efficacious OTC PPI products. The high consumptions of antacids and OTC ranitidine in the Pharmacy audit would seem to support this possibility.

Appropriate use of scarce healthcare resources

- The applicant claimed that the availability of OTC rabeprazole would alleviate pressures on the Medicare system, in particular time in GP surgeries, and that costs related to PBS funding of the drug would also be reduced.
- The evaluator asserted that such claims were supposition, as was the claim that advertising of rabeprazole would in effect increase the savings in scarce resources and costs. Concerning these, the evaluator argued that it would seem more likely that advertising of GORD and rabeprazole would channel more people to medical consultations, both via referrals from pharmacists and directly, and possibly increase (rather than decrease) unnecessary investigations.

Improved treatment outcomes and quality of life

- The evaluator accepted that OTC PPIs were a more effective treatment than antacids or H_2RAs. Increased use of PPIs, whether prescribed or OTC, might lead to improved treatment outcomes.

Decreased risk of injury, minimising the potential for misdiagnosis or under-treatment of patients with severe symptoms

- The application highlighted the existence of the PSA's guideline for "*Provision of pantoprazole as a Pharmacist only medicine*". A similar document for rabeprazole was promised. Attention was also drawn to the existence of other educational materials. The evaluator noted that none of this bore directly on the question of whether advertising should be permitted.

Decreasing potential inappropriate use for non-GORD indications

- The application invoked three factors – pharmacist involvement, pharmacist guidelines for provision and clear consumer focussed labelling – as contributing to mitigating the risk of consumers using the product inappropriately for non-GORD indications. The evaluator again noted that this did not bear directly on the question of whether advertising should be permitted.
- The evaluator also noted that an unaddressed issue was whether, if customer demand was driven by advertising, pharmacists would be able to maintain the level of their involvement and continue to implement guidelines.
- It was also stated that "Consumers are also easily able to access the CMI for further information on the use of their medicine." The submitted packaging indicated that the CMI was not included in the box ("Ask your pharmacist for a CMI"). The packaging directs to ask your doctor or pharmacist if you are taking digoxin or ketoconazole, but there was no mention of clopidogrel.

Proposed Education and Training Programmes by the sponsor

- The information provided indicates that a training programme will deal with GORD and diarrhoea. Whether or not the product is advertised is not relevant to the quality and usefulness of the proposed training. There was insufficient information to tell the extent to which important issues, such as possible interactions, would be addressed.

Compliance with legislated requirements

- The applicant included assurances that advertising, if permitted, would comply with regulations and the Therapeutic Goods Advertising Code.

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

Applicant's Response to the Evaluation Report

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

- Reiterated that rabeprazole and pantoprazole had a very similar safety and efficacy profile and that there would be some merit in considering these medicines as a group with regard to the possibility of an Appendix H entry.
- Noted the evaluator's inclination to the view that the information submitted supported that the advertising of the availability of PPIs might deliver a public health benefit, although it was difficult to quantify that benefit.

Response to 'areas of deficiency' identified by the evaluator

- The evaluator discussed two areas of deficiency in the submission: safety of rabeprazole relative to other PPIs; and the interaction between rabeprazole (and other PPIs) with clopidogrel and other thienopyridines. The applicant noted that no new data was allowable at this stage therefore the detail of the responses was necessarily limited.

Safety of rabeprazole relative to other PPIs

- Asserted that it was accepted that the similarity of PPIs in terms of efficacy generally extended to safety as well. In the first evaluation report and at the June 2010 meeting, it was acknowledged that rabeprazole itself was a generally safe and well tolerated drug. There was much clinical experience showing that rabeprazole had a good safety profile as well as a lower potential for certain drug interactions than some other PPIs (e.g. omeprazole) which were more extensively metabolized.
- Noted an overview of PPIs in GORD, in which the authors discussed the short and long term safety of PPIs and stated that the tolerability of PPIs as a group in both short term as well as longer term use had been good.
- Reiterated the expert comment provided by XXXXX, particularly the point that in recent years the adverse effects of regular dose long term PPI use had been highlighted but these data should not be extrapolated to short term, intermittent use of OTC PPIs.
- The conditions which may challenge safety were higher dosage, long term use and serious co-morbidities. OTC use of rabeprazole and other PPIs was confined to lower doses, for a short period of time. Patients who had serious pre-existing conditions were also likely to be seeing their doctor and pharmacist frequently for regular monitoring of their medical conditions.
- Reiterated that safety for use in the OTC setting had already been considered when creating the Schedule 3 entry and therefore detailed safety data were not provided as part of this application, which instead focused on the Appendix H issues.
- The evaluator also questioned the extent of exposure to rabeprazole in Australia. The applicant confirmed that an OTC rabeprazole product was launched in January 2011 and sales volumes had not been high enough to provide any meaningful post-

marketing safety data for Australia, although with time the applicant believed it would be able to do so. While there was much safety information on rabeprazole at prescription strength and dosages, this information could not be accurately extrapolated to OTC use.

Interactions

- The applicant advised that the potential interaction between rabeprazole and clopidogrel was discussed as part of the response to the previous evaluation. Clinical outcome and platelet inhibition studies have evaluated the potential for interaction between PPIs and clopidogrel. Conflicting views were reported and it was undetermined whether this interaction was a class effect.
- Clopidogrel is activated by the liver enzyme cytochrome P_{450} 2C19. However, not all PPIs interact with this enzyme in the same way, and rabeprazole, though metabolised by several cytochrome P_{450} isoenzymes, appears to be metabolised mainly by non-enzymatic reduction with minor CYP2C19 and CYP3A4 involvement.
- Reiterated previous advice that the European Medicines Agency, in a March 2010 statement "*Interaction between clopidogrel and PPIs*" recommended that the previous class warning for all PPIs be replaced with a warning stating that only the concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged. This followed new data which put into question the clinical relevance of interaction between PPIs as a class, and clopidogrel.
- The question of interactions was also raised by the TGA during the evaluation process and the TGA was satisfied that the general statement "*Ask your doctor before use if you are taking any other medicines*" covered the thienopyridine class of antiplatelet drugs as a whole. This matter was specifically discussed prior to the product's approval. The potential for interaction with thienopyridine antiplatelet drugs was similar for rabeprazole and pantoprazole, noting that pantoprazole also did not carry a specific interaction warning on its labelling. It was agreed, however, that reference to the clopidogrel interaction should appear in the CMI.
- The NSW Therapeutic Assessment Group have also produced a discussion paper and stated that there was no conclusive evidence about the clinical significance of the interaction and that further data was needed in order to address these concerns.

June 2011 Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX.

XXXXX supported the proposal to list rabeprazole in Appendix H.

XXXXX did not oppose the application for Appendix H listing of rabeprazole in principle, provided that a consistent approach was taken with respect to the requirements for demonstration of adequate Australian OTC data with individual PPIs before Appendix H listing was granted. In particular, noted that pantoprazole had a longer OTC

in-market use than rabeprazole, and that a recent request for Appendix H listing of pantoprazole was not successful.

Members noted a number of additional comments from XXXXX, as summarised below:

XXXXX

Argued that the safety profile; history of safe use; indication for short-term use; the ability of pharmacists to provide professional advice to ensure the quality use of medicines; the preparation of pharmacy through education and information provision; and the potential public health benefit resulting from increased awareness of all available treatments all combine to provide a sound justification for allowing advertising.

Asked that the proposal be considered in terms of the efficacy and safety of rabeprazole compared to other substances that were currently available and able to be advertised.

Argued that consumers stood to benefit through awareness of the options available to them, supported through mandatory intervention by pharmacists. Also provided various specific arguments in terms of the NCCTG advertising guidelines and section 52E:

NCCTG Schedule 3 advertising guidelines

- Argued that the NCCTG's guidelines had been met in relation to rabeprazole and provided comments in relation to the guideline criteria.

Potential public benefit

- Reiterated the argument that advertising would prompt consumers to seek advice from a pharmacist and that such advice may result in more effective treatment or earlier identification of consumers who require medical intervention.
- Suggested that inclusion in Appendix H would also potentially reduce unnecessary visits to GPs.
- Reiterated that, no matter what the effect of advertising, the consumer could not purchase the product except with the intervention of the pharmacist. Argued that this ought to be kept in mind when weighing the benefits of advertising against any potential risk that advertising may inappropriately influence demand.
- The ability to advertise will highlight the availability of rabeprazole in Schedule 3, while at the same time directing consumers to talk to a health professional about effective treatments for GORD.

Likelihood of advertising leading to inappropriate patterns of use

- Had seen no evidence, and could envisage no arguments, to suggest that advertising of rabeprazole would result in inappropriate use.

The wider regulatory system

- Reiterated that all advertising to consumers must comply with the *Therapeutic Goods Act 1989*, the Therapeutic Goods Regulations 1990 and the Therapeutic Goods

Advertising Code e.g. any rabeprazole advertising must be consistent with the registered indications, must comply with a range of general principles, must comply with the requirements for prohibited and restricted representations and must contain certain information (including the statement "Your Pharmacist's Advice Is Required").

The responsibility of pharmacists to be involved

· Educational tools and treatment protocols for PPIs had been prepared in order to ensure that pharmacists were able to provide appropriate professional advice.

Availability of CMI

· A CMI was available to assist pharmacists when counselling consumers.

Desire for consumers to manage their own medication

· Provided a general argument that consumers had a strong interest in accessing medical and pharmaceutical information and in taking control of their medication and treatment. In particular argued that the growth of the gastrointestinal category in supermarkets demonstrated the willingness of consumers in this category to manage their own medication.

Specific section 52E matters

(a) Risks and benefits

· Reiterated the favourable safety profile and benefits arguments above. Reiterated the regulatory compliance requirements for advertising. Also asserted that the risks of misuse were low and the safety of PPIs as a group was equivalent to that of H_2RAs, which were unscheduled and able to be advertised.

(b) Purposes for use

· Noted that the purpose, relief of heartburn and other symptoms of GORD, was capable of being communicated to consumers via advertising.

(c) Toxicity

· Rabeprazole had a well documented safety profile.

(e) Potential for abuse

· Was unaware of any evidence that rabeprazole was associated with dependence, abuse or illicit use.

XXXXX

· Noted that a Schedule 3 rabeprazole product was only launched in January 2011. As such there were limited in-use data that could inform considerations such as risks and benefits, potential hazards, extent and pattern of use and other relevant matters in the context of advertising and public health benefit.

- Proposed that Appendix H listing of rabeprazole should only be granted at a time when sufficient in-market use and pharmacist experience with this medicine had been obtained.
- However, if rabeprazole was determined to be suitable for Appendix H, then this listing should also extend to pantoprazole; which had greater in-market use. The submission reiterated the previous argument that pantoprazole had demonstrated a potential for public benefit from advertising.

June 2010 NDPSC Consideration – Rabeprazole

Members noted that the June 2010 evaluation report recommended rejection of the requested Appendix H listing, specifically stating that:

- The evaluator remained unconvinced that advertising of OTC rabeprazole would lead to greater public health benefits.
- Compared to the failed application one year ago, scant new evidence was provided to support the current resubmission.
- Advertising of any OTC PPIs should be precluded until safety concerns surrounding potential pharmacokinetic interactions between PPIs and thienopyrydines were disproven.

Members also noted the following from the June 2010 NDPSC discussion:

- Members agreed that the advertising of rabeprazole would not reduce consultation costs and could facilitate an increase in unnecessary investigations.
- Although Members noted growing evidence that potential interactions with antiplatelet medication could be limited to omeprazole, it was generally agreed that there was still insufficient evidence of public health benefit of advertising rabeprazole.
- Members discussed the level of consumer awareness of the availability of GORD treatments. A Member asserted that due to the general sale and Schedule 2 availability of other products for the same indication, there was limited consumer awareness of PPIs. The Member further asserted that the public would not generally seek advice from a pharmacist for GORD and therefore remain unaware of possible alternative treatments. Another Member asserted that methods other than Appendix H listing could be used to raise public's awareness of GORD and the range of available treatments.

2011 Pantoprazole Considerations

Members noted the following from the February 2010 ACMS discussion:

- Members questioned the benefit of advertising of PPIs. A Member asserted that if pantoprazole was included in Appendix H, a consistent approach should be maintained for all PPIs to ensure awareness of multiple treatments. Another Member

contended, however, that the aim of product advertising was to increase product awareness (and resultant market share), not to improve community awareness of a disease and all its available treatments. The Member noted that a television campaign aimed at increasing the awareness of GORD currently existed and an Appendix H listing for PPIs would not provide additional benefit to the public's awareness of available forms of treatment.

- A Member asserted that GORD required diagnosis by appropriately qualified practitioners (i.e. pharmacists). The Member also stated that unlike H_2RAs, there was a risk that pantoprazole could mask symptoms of more serious disorders and advice was required before a treatment was selected. It was asserted that advertising of pantoprazole would transfer the responsibility of diagnosis onto the consumer which may inappropriately increase pressure on the pharmacist for supply of this product.
- Members also noted that PPI efficacy relies on consistent use over a longer period of time. A Member asserted that advertising may inadvertently reinforce inaccurate consumer expectations that PPIs, like some other GORD treatments, may be used as a "quick fix" and would not require adherence to treatment.

Members also noted the following points from the delegate's reasons for deciding to support the February 2011 ACMS recommendation to not list pantoprazole in Appendix H:

- The delegate noted a further submission's comment in relation to factors outlined in the NCCTG Guidelines for brand advertising of substances included in Schedule 3. The delegate noted section 32 of Part 3 of the SUSMP stating that Schedule 3 substances are not allowed to be advertised unless listed in Appendix H. The delegate clarified that inclusion of a Schedule 3 substance in Appendix H was by exception following consideration of the substance's specific risk-benefit profile.
- The delegate reiterated the ACMS comment that the factors listed in the SPF guidelines were meant as a guide and inclusion of a Schedule 3 substance in Appendix H should not be assumed based only on these. The delegate asserted that the balance between potential public health benefit and the protection of public health and safety was fundamental to these considerations.
- The delegate also reiterated concerns raised in a pre-meeting submission in relation to the effect of advertising on a consumer's decision-making in choosing medicines.

Other Matters

The Committee noted that there had been some recent literature regarding a possible link between PPIs and fracture risk, which may or may not be relevant to the Appendix H consideration. In particular, the May/June issue of the *Annals of Family Medicine* discusses the results of a meta-analysis on this issue, which concluded that there was possible evidence linking PPI use to an increased risk of fracture (accessible at www.annfammed.org/cgi/reprint/9/3/257).

An accompanying editorial discussed balancing the risks and benefits of PPIs and concluded that PPIs have clear benefits in patients that require them, and they should not be denied to patients who are likely to benefit from them. On the other hand, long-term PPI exposure may lead to other unwanted effects and should be reserved for patients likely to benefit from them. They should not be used long-term for undifferentiated dyspepsia, but neither should they be denied for patients with established persistent GORD, NSAID risk, and hypersecretory states, while aiming for the lowest effective maintenance dose. The article is accessible at www.annfammed.org/cgi/reprint/9/3/200.

EXPERT ADVISORY COMMITTEE DISCUSSION

XXXXX.

Several Members noted the limited experience on the Australian market with Schedule 3 supply of rabeprazole and argued that this was insufficient to support an Appendix H listing. The Members also recalled the recent decision to not support an Appendix H listing for pantoprazole, which had significantly more Australian experience with Schedule 3 supply.

A Member noted the evaluator's concern regarding the lack of public health data for Schedule 3 supply of rabeprazole and argued that this was hard to generate when the product could not be advertised. Other Members argued that this in fact largely reflected the limited time that a Schedule 3 rabeprazole product had been in the Australian market and was yet a further reason that consideration of an Appendix H entry would be premature.

Members also revisited the reasons for not supporting recent requests for Appendix H listing for various PPIs and agreed that there remained unaddressed concerns. Members recalled that the scheduling policy default for Schedule 3 substances is to not allow advertising, and the onus was on the applicant to establish the public benefit from advertising. Members generally agreed with the evaluator that the case for the public benefit from advertising rabeprazole had not been sufficiently made.

A Member also noted that the expert opinions referenced by the applicant had supported targeted education, which was not necessarily the same as supporting branded advertising. Several Members noted recent examples of consumer awareness campaigns which did not rely on branded advertising.

Other matters

The Committee noted that the reports of a link between PPI use and fractures, while of interest, appeared to be linked to long term use of PPIs and were therefore of limited relevance to the short term Schedule 3 supply of rabeprazole.

DELEGATE'S INTERIM DISCUSSION

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

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (f) any other matters considered necessary to protect public health.

DELEGATE'S INTERIM DECISION

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

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

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

PART B – FINAL DECISIONS ON MATTERS NOT REFERRED TO AN ADVISORY COMMITTEE

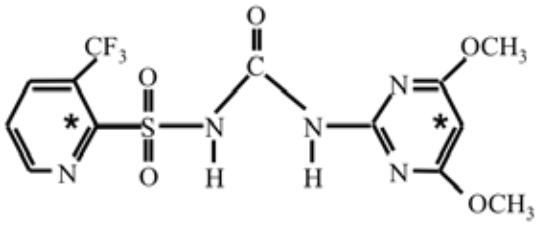
3. CHEMICALS

3.1 FLAZASULFURON

BACKGROUND

Flazasulfuron is a member of the pyrimidinyl sulfonylurea class of chemicals. The mechanism of herbicidal activity for the sulfonylurea class of chemicals is by inhibiting acetolactate synthase, a key enzyme in the synthesis of several amino acids in plants which do not exist in mammalian systems. This process results in slow or stunted plant growth and/or ultimate plant death.

The IUPAC name for flazasulfuron is 1-(4,6-dimethoxpyrimidin-2-yl)-3-(3-trifluoromethyl-2-pyridylsulphonyl)urea and the structure is:



XXXXX submitted data to the APVMA seeking approval of the active ingredient flazasulfuron. XXXXX.

XXXXX Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for flazasulfuron. A delegate agreed that this was a matter for a scheduling consideration. The delegate decided that this matter did not require advice from the ACCS as the proposal was straight forward, the key data was robust, several other similar substances were already scheduled and there was no apparent potential for requiring additional controls through SUSMP Appendices or for unintended regulatory impact.

SCHEDULING STATUS

Flazasulfuron is not currently specifically scheduled. Several other sulfonylurea pesticides are listed either in Appendix B (including bensulfuron-methyl, metsulfuronmethyl) or Schedule 5 (including sulfometuron-methyl, chlorsulfuron and thifensulfuron). Flazasulfuron has a similar structure to some of these other sulfonylurea pesticides, but it could not be considered to be a "derivative" under the SUSMP definition.

SUBMISSIONS

Applicant's submission

The XXXXX Assessment Technical Report on XXXXX APVMA submission recommended a Schedule 5 listing without a cut-off for flazasulfuron based on the toxicity profile (low acute oral, dermal and inhalational toxicity and not a skin irritant or skin sensitiser but was a slight eye irritant).

Other XXXXX conclusions included:

- The ADI was established at 0.013 mg/kg bw/d, based on a NOEL of 1.3 mg/kg bw/d in a XXXXX-year dietary study in XXXXX using a default 100-fold safety factor.
- No ARfD was established for flazasulfuron because no significant treatment related findings had been observed in experimental animals following a single dose administration of flazasulfuron.
- The applicant had seen a copy of the evaluation report and informed the evaluator that they had no comments on the evaluator's scheduling proposal.

Toxicology of flazasulfuron

XXXXX

- Flazasulfuron had a low acute oral XXXXX dermal XXXXX, and inhalational XXXXX toxicity in XXXXX. It was a slight eye irritant but was not a skin irritant in rabbits and was not a skin sensitiser in XXXXX.
- Eye irritation: An eye irritation study conducted in XXXXX resulted in conjunctivae with individual redness, chemosis and/or discharge at XXXXX post-exposure. Additionally, conjunctival reddening persisted until XXXXX after exposure in XXXXX animals. All symptoms of eye irritancy had completely resolved in all animals by XXXXX. Based on these observations, the evaluator concluded that flazasulfuron was considered to be a slight eye irritant in XXXXX.
- Dermal toxicity: In an acute dermal toxicity study, XXXXX were treated with either XXXXX of flazasulfuron. There were no mortalities or clinical symptoms, with animals gaining bodyweight during the study, and findings at necropsy were unremarkable. The evaluator noted that despite minor limitations in reporting, this study was considered to be suitable for regulatory purposes and concluded that under the conditions of this study, the acute dermal toxicity of flazasulfuron was low as determined in XXXXX.
- Developmental toxicity: A developmental toxicity study carried out on XXXXX with flazasulfuron concentrations of XXXXX resulted in decreased foetal body weight, and an increase in foetal mortality, unossified metatarsals, external 14th rib and splitting or dumbbell shape of the thoracic vertebrae. The evaluator asserted that these were a secondary non-specific consequence of marked maternal toxicity, as

indicated by large decreases in food consumption and body weight gain, including a body weight loss on days 6-9 of gestation. In another developmental study conducted on XXXXX with flazasulfuron concentrations of XXXXX resulted in decrease in live foetuses and mean litter size due to an increase in aborted litters, and a single instance of agenesis of the pulmonary artery. The evaluator asserted that in the absence of historical control data it was assumed that this was treatment related, being a secondary non-specific consequence of marked maternal toxicity, as indicated by decreased food consumption, food use efficiency and bodyweight loss over 6 days of the dosing period. The evaluator therefore concluded that flazasulfuron was not a developmental toxicant in XXXXX.

- No evidence of mutagenicity potential for flazasulfuron in XXXXX. A negative result was also seen in an XXXXX. The evaluator concluded that the available data indicates flazasulfuron was not a genotoxicant.
- No data was provided by the applicant to assess the neurotoxicity of flazasulfuron, though no evidence of such was seen in the submitted studies.
- No evidence of carcinogenic potential in either sex at any of the dose level tested in XXXXX.
- No treatment related effect on reproductive parameters in a XXXXX study.

Systemic effects

- Repeat dose studies in XXXXX had shown that the toxic effects of flazasulfuron pertain mainly to decreased bodyweight gain, food consumption, food use efficiency, and increased incidence of haemolytic anaemia, and altered kidney and liver histopathology.
- In XXXXX the liver was the target organ for toxicity, while in XXXXX it was the kidney, with kidney and liver toxicity being seen at higher dose levels in XXXXX respectively. Non-haemolytic anaemia consisting of reduced haemoglobin, erythrocyte counts, and haematocrit was observed at levels at or above those causing effects on the liver and kidney, and was not considered to be related to the haemolytic anaemia that resulted from the direct binding to haemoglobin and subsequent haemolysis as described for other pyrimidinyl sulfonylurea herbicides.
- Atrophy of the testes was also seen at high doses in the chronic dietary study in XXXXX, but was within the high spontaneous rate and was not considered to be related to the test material.
- The evaluator indicated that the chronic toxicity study conducted in XXXXX noted the presence of hyaline droplets in the proximal tubules of males and the study considered that the mechanism for the observed kidney toxicity in males was due to a2m-globulin, and as such was XXXXX specific mechanism that was not applicable to humans. The evaluator, however, noted that the available information did not support this proposed rationale. In addition to the chemical nature of the detected crystalline material in the urine not being determined, kidney toxicity was also seen in females. The evaluator concluded that it had not been sufficiently demonstrated that

the observed kidney findings in XXXXX were due to a2m-globulin and not applicable to humans.

Sub-chronic studies

- In a XXXXX-week oral dosing study, XXXXX received XXXXX of flazasulfuron. Clinical symptoms of toxicity were confined to one male at XXXXX that was sacrificed *in-extremis* on week 11, with the animal lacking stools and having reduced spontaneous motor activity. Necropsy in this animal found hemosiderin deposition in hepatocytes and interstitial tissue, hepatocellular necrosis, degeneration and bile duct proliferation, and liver effects in the form of an 'accentuated lobular pattern', hardening and 'depressed areas'. Changes in bodyweight were confined to XXXXX at XXXXX. However, the overall magnitude of the decrease was not considered to be toxicologically significant. Furthermore, as food intake was unaffected it was considered likely that the slight decrease seen in body weight gain was probably caused by decreased food use efficiency (though no such data was available).
- The NOEL in XXXXX was XXXXX and in XXXXX was XXXXX, in both instances based on and inflammatory cell infiltration and hemosiderin deposition in the liver at XXXXX.

Other matters

- The evaluator noted that the use of sulfonylurea medicines in humans was associated with haemolysis as a result of the chemicals binding to erythrocyte haemoglobin, with subsequent anaemia and changes in haematopoiesis. Very similar effects were seen in laboratory mammals in a number of toxicity studies with sulfonylurea herbicides, but typically at high doses only. This inhibition was considered to cause compensatory effects such as increased haematopoiesis, and increased spleen weights. Another, common effect of sulfonylurea herbicides in laboratory animals was centrilobular hepatocellular hypertrophy and subsequent increases in liver weights, which was stated to be caused by increased glycogen accumulation in the liver and/or as a general adaptive response to xenobiotic agents.
- The pyrimidinyl sulfonylurea herbicides had been associated with bladder epithelia tumours, as a result of precipitation to form calculi in the bladder when administered at high doses and subsequent mechanical injury (i.e. a non-genotoxic mechanism). This finding had been consistently identified in rats, mice, and dogs. The evaluator indicated that the mechanism of bladder injury and tumourigenesis, and its relevant to humans, had been discussed extensively by a working group called the "Rodent bladder carcinogenesis working group". The evaluator indicated that the working group pointed out that although urinary tract stones were common in humans and the cellular structure of the urothelium was similar in rodents and humans, bladder tumours in humans were rarely associated with stones. Anatomical differences between rodents and humans predispose the residence and accumulation of precipitates in the rodent bladder and injury to the bladder epithelium, whereas in

humans, xenobiotics had a diminished potential for damage to the bladder epithelium and an increased likelihood of being passed during urination.

- The evaluator further indicated that more recently, urinary tract bladder tumours associated with urinary-tract calculi were assessed in the International Programme on Chemical Safety (IPCS) Framework for human relevance analysis of information on carcinogenic modes of action which concluded that humans were less susceptible to the carcinogenic effects of calculi than rodents for this non-genotoxic mode of action. The evaluator concluded that bladder carcinogen acting via formation of calculi should not pose a carcinogenic hazard to humans provided that intake was below the threshold concentration required for generation of urinary precipitates.

Hazard classification

- The evaluator indicated that with the available toxicology information, flazasulfuron had not been classified as a hazardous substance according to NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), and no human health risk phrases would be required for this active constituent.

DELEGATE'S DISCUSSION

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

The delegate noted that flazasulfuron had low acute toxicity via oral, dermal, and inhalational routes. It was not a skin irritant or a skin sensitiser. It was, however, a slight eye irritant. The delegate therefore concluded that the toxicity profile of flazasulfuron aligned with the Scheduling Policy Framework factors for Schedule 5. The delegate further decided that a cut-off to exempt from scheduling was not appropriate at this time as no data indicative of an appropriate cut-off level, such as might be generated from a product approval process, had been received.

As a separate matter, the delegate also noted that while not currently specifically scheduled, flazasulfuron was similar to several other sulfonylurea substances that are listed in Schedule 5, both structurally and in its mode of action. The delegate agreed that for clarity and in line with recent practice that a specific scheduling entry for flazasulfuron was necessary.

DELEGATE'S FINAL DECISION

The delegate decided to include flazasulfuron in Schedule 5. The delegate also decided that an implementation date of 1 January 2012 was appropriate (i.e. three months after the publication of the final decision).

Schedule 5 – New entry

FLAZASULFURON.

4. MEDICINES

4.1 CABAZITAXEL

BACKGROUND

Cabazitaxel is a tubulin-binding taxane semi-synthetic drug with antitumour activity in docetaxel-resistant cancers. It shares the same basic structure as paclitaxel and docetaxel. It affects the mitotic spindle and microtubules of cells by binding to free tubulin of cells.

Cabazitaxel has been investigated for use in combination with prednisone or prednisolone, in the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

SCHEDULING CONSIDERATION

The delegate noted that:

- As cabazitaxel is not scheduled in Australia, this is a consideration of scheduling of a new chemical entity as outlined in the Scheduling Policy Framework.
- Other taxanes are specifically scheduled (docetaxel is listed in Schedule 4) and a specific entry for cabazitaxel would ensure clarity in enforcement of restrictions.
- Cabazitaxel is not currently scheduled in New Zealand.
- Cabazitaxel has been approved as prescription medicines by the USFDA and the European Commission.
- The seriousness of the indication mandates interaction with a medical professional.
- There is limited experience in the use of cabazitaxel in the Australian environment.
- There is no available data suggesting abuse / misuse potential which would warrant a Schedule 8 entry.
- Cabazitaxel is associated with greater toxicity than mitoxantrone leading to treatment discontinuation. Reported adverse reactions from clinical trials include severe neutropenia, and fatigue, asthenia, nausea, vomiting, diarrhoea, haematuria and peripheral neuropath.
- Although there is some evidence of pregnancy effects in animals associated with cabazitaxel, given the proposed indication, treatment would always occur under the direction of a medical specialist and an Appendix D entry would not be required.
- There was no evidence of sedation effects which would warrant an Appendix K entry.

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

DELEGATE'S FINAL DECISION

The delegate decided to list cabazitaxel in Schedule 4, with an implementation date of 1 January 2012.

Schedule 4 – New Entry

CABAZITAXEL.

4.2 CATUMAXOMAB

BACKGROUND

Catumaxomab is a rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule EpCAM, which is overexpressed in most carcinomas, the CD3 antigen; and a third binding site that enables interaction with accessory immune cells. It differs from previous monoclonal antibodies by its trifunctional properties against tumour cells.

Catumaxomab has been investigated for use in the treatment of malignant ascites in patients with EpCAM-positive carcinomas.

SCHEDULING CONSIDERATION

The delegate noted that:

- While captured by the Schedule 4 group entry for monoclonal antibodies, catumaxomab has not been specifically scheduled in Australia, so this is a consideration of scheduling of a new chemical entity as outlined in the Scheduling Policy Framework.
- Several other monoclonal antibodies are specifically scheduled (adalimumab and belimumab are listed in Schedule 4) and a specific entry for catumaxomab would ensure clarity in enforcement of restrictions.
- Catumaxomab is not currently scheduled in New Zealand.
- Catumaxomab is approved as prescription medicine in the EU (April 2009) for treatment of malignant ascites. The USFDA granted orphan drug status for catumaxomab in September 2006 for ovarian cancer and in January 2009 for gastric cancer.
- The seriousness of the indication mandates interaction with a medical professional.
- There is limited experience in the use of catumaxomab in the Australian environment.
- There is no available data suggesting abuse / misuse potential which would warrant a Schedule 8 entry.
- The most frequent adverse events (AE) associated to catumaxomab were pyrexia, abdominal pain, nausea and vomiting. The most frequent severe AE considered

related to catumaxomab were abdominal pain, lymphopenia, serum GGT increase and pyrexia. Associated serious AE were ileus, pyrexia, subileus and abdominal pain.

- The medicinal product should not be used during pregnancy unless clearly necessary, given that is unknown whether catumaxomab is excreted in human breast milk. However, as the proposed indication treatment would always occur under the direction of a medical specialist, an Appendix D entry would not be required.
- There was no evidence of sedation effects which would warrant an Appendix K entry.

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

DELEGATE'S FINAL DECISION

The delegate decided to list catumaxomab in Schedule 4, with an implementation date of 1 January 2012.

Schedule 4 – New Entry

CATUMAXOMAB.

4.3 IPILIMUMAB

BACKGROUND

Ipilimumab is a monoclonal antibody under investigation for the treatment of melanoma, prostate cancer, lung cancer, and various other solid tumours.

SCHEDULING CONSIDERATION

The delegate noted that:

- As ipilimumab is not specifically scheduled in Australia, this is a consideration of scheduling of a new chemical entity as outlined in the Scheduling Policy Framework (SPF). According to the SPF, the delegate may make a final decision on the scheduling of this substance without referring the matter to an advisory committee.
- Although ipilimumab is captured by the Schedule 4 group entry for monoclonal antibodies, many other monoclonal antibodies are specifically listed in Schedule 4 and an individual entry would provide clarification for enforcement.
- Ipilimumab is not currently scheduled in New Zealand. Ipilimumab was approved for the treatment of unresectable or metastatic melanoma in the US in March 2011.
- The seriousness of the indication mandates interaction with a medical professional.
- Adverse effects include enterocolitis, hypophysitis, dermatitis, arthritis, uveitis, hepatitis, nephritis, and aseptic meningitis.

- There is limited experience in the use of ipilimumab in the Australian environment.
- There was no evidence to suggest abuse / misuse potential which would warrant a Schedule 8 entry. There was no evidence of sedation effects to warrant an Appendix K entry, nor pregnancy effects which would warrant Appendix D or L entries.

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

DELEGATE'S FINAL DECISION

The delegate decided to list ipilimumab in Schedule 4, with an implementation date of 1 January 2012.

Schedule 4 – New Entry

IPILIMUMAB.

5. EDITORIALS AND ERRATA

5.1 FEXOFENADINE

Fexofenadine - Errata

Following publication of the June 2011 delegate's final decision to exempt certain preparations of fexofenadine from scheduling, a request from the TGA was received to editorially amend the entry to better reflect the intent of the scheduling decision.

The June 2011 decision states:

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

The current scheduling of fexofenadine, as implemented from 1 September 2011, states:

Schedule 2

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

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

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

Schedule 4

FEXOFENADINE **except**:

(a) when included in Schedule 2; or

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

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

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

The delegate noted that the intent of the June 2011 decision was to only exempt up to 5 days supply of the specific fexofenadine preparation. However, it was subsequently noted that a literal reading of the new fexofenadine entry implied that it would be possible for a product containing 10 dosage units of 120 mg each (i.e. 10 days supply) to be exempt from scheduling.

The delegate noted that inclusion of a reference to not more than 5 days supply in the Schedule 2 and 4 entries would better reflect the intent of the original scheduling decision.

The delegate considered the implementation date for the editorial amendment. It was noted that as the editorial amendment only clarified the intent of the original June 2011 decision it would not adversely affect stakeholders. The delegate agreed that the fexofenadine editorial amendment should have a retrospective implementation date of 1 September 2011.

DELEGATE'S FINAL DECISION

The delegate decided to editorially amend the Schedule 2 and 4 fexofenadine entries to specifically stipulate a limit of 5 days supply in the exemption.

The delegate decided on a retrospective implementation date of 1 September 2011 for the above editorial amendment.

Schedule 2 – Amendment

FEXOFENADINE – Amend entry to read:

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

(a) in a primary pack containing 10 dosage units or less and not more than 5 days supply; and

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

Schedule 4 – Amendment

FEXOFENADINE – Amend entry to read:

FEXOFENADINE **except**:

(a) when included in Schedule 2; or

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

(i) in a primary pack containing 10 dosage units or less and not more than 5 days supply; and

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