Final decisions & reasons for decisions by delegates of the Secretary to the Department of Health

November 2013

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

A delegate of the Secretary to the Department of Health 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.

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the July 2013 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#8);
- scheduling proposals initially referred to the July 2013 meeting of the Advisory Committee on Medicines Scheduling (ACMS#9);
- scheduling proposals initially referred to the July 2013 joint meeting of the ACCS and the ACMS (joint ACCS-ACMS#6);
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

- The first 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 24 April 2013 at http://www.tga.gov.au/newsroom/consult-scheduling-acms-1307.htm and the second public notice was published on 13 June 2013 at http://www.tga.gov.au/newsroom/consult-scheduling-accs-1307.htm.
- Redacted versions of the public submissions received in response to this invitation were published on 23 May 2013 at http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

Interim decisions

- The delegates' interim decisions on recommendations by the ACCS#8, ACMS#9 and joint ACCS-ACMS#6 were published on 26 September 2013 at http://www.tga.gov.au/industry/scheduling-decisions-1307-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.

- 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, may not be considered by the delegate.
- Redacted versions of public submissions received in response to the interim decisions were published on 8 November 2013 at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Final decisions

- In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either confirming varying or setting aside the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling application to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer an application to an expert advisory committee for advice, the delegate considers the scheduling guidelines as set out in the Scheduling Policy Framework (SPF) accessible at <http://www.tga.gov.au/industry/scheduling-spf.htm>.

Implementation

The SUSMP and its amendments are available electronically at the ComLaw website, a link to which can be found at <http://www.tga.gov.au/industry/scheduling-poisons-standard.htm>.

Table of contents

Glossary

Abbreviation	Name
AAN	Australian Approved Name
AC	Active constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable daily intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

Abbreviation	Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
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

Abbreviation	Name
INN	International Non-proprietary Name
ISO	International Standards Organization
LC50	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.
LD50	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 (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])

Abbreviation	Name
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (formerly 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

Abbreviation	Name
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 expert advisory committee

1. Scheduling proposals referred to the July 2013 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#8)

1.1 1,2 – BENZENEDIOL (CATECHOL)

Scheduling proposal

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) process, recommended the scheduling delegate consider including cosmetic preparations and domestic preparations containing 1,2-benzenediol in Appendix C and in Schedule 6/7, respectively.

NICNAS indicated that the oral and dermal toxicity, sensitisation and eye irritation potential of this substance met Schedule 6 factors of the Scheduling Policy Framework (SPF). The potential for carcinogenicity appears to meet the Schedule 7 factors of the SPF. In addition, the risk cannot be mitigated by warnings or packaging, as the potential use in cosmetics involves direct dermal application.

The Chemicals Scheduling Delegate considered a proposal to include 1,2-benzenediol for domestic use in Schedule 6 or Schedule 7 and preparations containing 1,2-benzenediol for cosmetic use in Appendix C. This proposal also includes consideration of appropriate cut-offs for exemption from scheduling.

The delegate considered the NICNAS proposal for a new schedule entry for 1,2-benzenediol in Schedule 7 on the basis of potential carcinogenicity. The delegate noted that the Scheduling Policy Framework (SPF) indicates that proposals for listing in Schedule 7 should be considered by the ACCS. Accordingly, the delegate referred the application to the July 2013 Advisory Committee on Chemicals Scheduling (ACCS) meeting.

The delegate sought the following specific advice from the ACCS:

- Is the more appropriate listing in Schedule 6, based on acute toxicity, skin/eye irritancy and skin sensitisation potential, or Schedule 7 based on potential carcinogenicity?
- Is there sufficient basis for establishing a cut-off to a lower schedule for such an entry? While 1,2-benzenediol does not meet the boiling point criterion (<220^{o}C) for the Schedule 6 phenol entry, would the exemption cut-off value (3%) for phenol be appropriate for 1,2-benzenediol?
- Is listing in Appendix C an appropriate measure for controlling use in cosmetics and personal care products, with a listing cut-off established at X%, and should such listing in Appendix C be additional to any controls imposed under Schedule 6/7 listing?
- Are there likely to be any unintended consequences of any scheduling recommendation, with inadvertent capture of retail chemical products other than cosmetics and personal care products?
- Can ACCS advise on appropriate wording for a Schedule 6 and/or Appendix C listing, including whether the substance be listed with its approved chemical name (1,2-benzenediol) and the common name ‘catechol’?

Substance details

The chemical appearance of 1,2-benzenediol[1] (catechol) is colourless crystals, discolours to brown on exposure to air and light, especially when moist. It has faint characteristic (phenolic) odour and sweet and bitter taste.

1,2-benzenendiol (catechol) has been reported uses such in cosmetic products (i.e. hair dyes, perfumes and essential oils), domestic (surface treatments) and in commercial use (i.e. photographic developer, colouring agents, as ingredient in epoxy coatings and adhesives).

Toxicity	1,2-benzenediol	SPF[2] Classification
Oral LD_{50} (mg/kg bw)	300	Moderate to high
Dermal LD_{50} (mg/kg bw)	600	Moderate to high
Inhalational LC_{50} (mg/m^3/4 h)	2800	Moderate to high
Skin irritation	Irritant	
Eye irritation	Irritant	
Skin sensitisation	Sensitiser	

Observations in humans

An epidemiology study reported exposure of 13 workers in a chemical factory in Japan to catechol (2 to 72 ppm) and phenol (55 to 260 ppm) vapours over 2 years (OECD 2003b). The clinical examinations and physical responses of workers indicated significant cough, sputa, throat and eye irritation.

Repeat dose toxicity

In the only available reliable repeated dose oral toxicity study in rats (Wistar) following the guideline OECD 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test), the substance was administered via gavage to 10 animals/sex/dose at 0, 30, 80 and 160 mg/kg bw/day for 4 weeks to males and 7 weeks to females. Mortality was observed at the highest dose in 2 males and 1 female (ECHA 2012). Tremors were observed at the highest dose. At the two highest doses the incidence and severity of squamous hyperplasia in the stomach were increased in animals of both sexes. A no observed adverse effect level (NOAEL) of 30 mg/kg bw/day can be derived based on squamous hyperplasia in the stomach.

Genotoxicity

The genotoxic potential of the chemical is summarised from the conclusion of the OECD (2003a). The chemical appeared to show generally negative results in point mutation studies but uniformly positive result in clastogenicity studies. There is sufficient evidence to classify the chemical as causing possible mutagenic effects.

Carcinogenicity

Classified by the International Agency for Research on Cancer (IARC) as Group 2B (possibly carcinogenic to humans) based on sufficient evidence of carcinogenicity in experimental animals (IARC 1999).

[1] NICNAS (2013): Inventory Multi-tiered Assessment and Prioritisation (IMAP). Human Health Tier II Assessment for 1,2-benzenediol. <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=2>

[2] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

The chemical was tested for carcinogenicity by oral administration in one study in mice and in two studies in rats. No increase in the incidence of malignant tumours was found in mice (IARC 1999). In rats, it induced adenocarcinomas in the glandular stomach in several strains. In one study (ECHA 2012, Environment and Health Canada, 2008) administration of the chemical in the diet in male rats for 34 weeks caused hyperplasia and adenomas of the pyloric gland (glandular hyperplasia) at 141 or 318 mg/kg bw/day. Very weak hyperplasia was noted at 33 and 65 mg/kg bw/day. However, after a 2-year exposure, adenomas and submucosal hyperplasia of the glandular stomach were found in nearly all animals at 33 mg/kg bw/day and higher doses.

Reproductive and developmental toxicity

Any reproductive and developmental effects were only observed secondary to maternal toxicity, so the chemical is not a specific reproductive or developmental toxin.

Scheduling status

1,2-benzenediol is not specifically scheduled.

Scheduling history

1,2 –benzenediol (catechol) has not been considered for scheduling before.

Public pre-meeting submissions

One submission was received supporting in principle the internationally aligned risk management of catechol. The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

ACCS advice to delegate

The Committee recommended that preparations containing 1,2-benzenediol be included in Schedule 6 and a cross-reference be added to the Index of the SUSMP.

The Committee also recommended an implementation date of 1 February 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance.

The reasons for the recommendation comprised the following:

- Benefit for industrial use.

Delegate's interim decision

The Delegate accepts the advice tendered by the ACCS and agrees to include a new entry for 1,2-benzenediol in S6, with a cross-reference in the SUSMP index to the common name, catechol.

An implementation date of 1 February 2014 is also agreed, since it appears there may be no products on the Australian market that require re-labelling.

The Delegate notes, and accepts, ACCS advice that the listing of 1,2-benzenediol in Appendix C for cosmetic use is not warranted, in that controls imposed via Schedule 6 listing should limit the use of this chemical in cosmetic products, and achieve appropriate label warnings (POISON signal heading) for any products formulated with this ingredient. This is reinforced by the ACCS recommendation that no scheduling cut-off be implemented.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* includes (c) toxicity and (d) dosage, formulation, labelling, packaging and presentation of a substance:

- The acute and chronic toxicity profile of 1,2-benzenediol is consistent with S6 scheduling criteria in the SPF.
- The primary objective of this scheduling application was to consider controls over the use of 1,2-benzenediol in cosmetic preparations. However, the schedule entry is also applicable to any other types of products that may be sold to the general public. Scheduling is not intended to replace controls over hazards and information provided to industrial users of the chemical.

The ACCS advice does not include any proposal to develop First Aid (Appendix E) or warning statements/safety directions (Appendix F). Although there may not currently be any products in the Australian retail market place, the following proposed entries in Appendices E & F provide for consistency with scheduling of S6 substances with hazard profiles comparable to that of 1,2-benzenediol.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (available at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=2);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[3]; and
- other relevant information.

Submissions on Interim Decision

No public submissions were received.

Delegates final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

Schedule 6 – New entry

1,2-BENZENEDIOL.

SUSMP Index – New cross-reference entries

CATECHOL

See 1,2-BENZENEDIOL

[3] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

Appendix E, Part 2

POISON	STANDARD STATEMENT
1,2-benzenediol (catechol)	A,E1,S1

Appendix F, Part 3

POISON	WARNING STATEMENT	SAFETY DIRECTION
1,2-benzenediol (catechol)	51, 59	1, 4, 8

1.2 3-IODO-2-PROPYNYL BUTYL CARBAMATE (IODOCARB)

Scheduling proposal

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) process, recommended the scheduling delegate consider including preparations containing 3-iodo-2-propynyl butyl carbamate (iodocarb) in Appendix C.

The NICNAS's scheduling recommendation noted that the sensitising potential of iodocarb indicates that an appropriate parent schedule is Schedule 6, although a cut-off to unscheduled is warranted. For cosmetic application, relevant cut-offs may be the previous European Union (EU) limit of 0.05% or the United States (US) Cosmetic Ingredient Review CIR recommendation of 0.1%. It may be noted that the International Fragrance Association (IFRA) Quantitative Risk Assessment (QRA) calculations based on EU Cosmetic Directive limits showed that, under the assumptions of this method, the consumer exposure level was less than the acceptable exposure level for the majority of uses.

The Chemicals Scheduling Delegate considered a proposal to amend the current Schedules 5 and 6 iodocarb entries to include cosmetic preparations containing iodocarb in Appendix C. This consideration also includes whether an Appendix C exemption cut-off for cosmetic preparations containing 0.05 per cent or 0.1 per cent iodocarb is appropriate.

The delegate considered the NICNAS proposal for amending the current entries for iodocarb in Schedules 5 and 6 to include cosmetic preparations containing iodocarb in Appendix C. This consideration also includes whether an Appendix C exemption cut-off for cosmetic preparations containing 0.05 per cent or 0.1 per cent iodocarb is appropriate.

The delegate's reasons for referring this to the Advisory Committee on Chemicals Scheduling (ACCS) included:

- While iodocarb is currently listed in Schedules 5 and 6, with exemptions for aqueous products containing 10% or less, the NICNAS IMAP submission specifically requests consideration of appropriate controls over its use in cosmetics and personal care products, via a possible listing in Appendix C. This type of application requires advice from the ACCS.

Accordingly, the delegate referred the application to the July 2013 ACCS meeting.

The delegate sought ACCS's advice on the following issues:

- Does the NICNAS IMAP submission warrant an additional entry in Appendix C, to control the use of iodocarb as a preservative in cosmetics and personal care products? If so, should an exemption cut-off of 0.1% or 0.05% be applied?
- To what extent should any Appendix C entry refer to products that could be aerosolised?
- If some jurisdictions apply controls consistent with listing in Schedule 7 for substances listed in Appendix C, is there potential for conflict with the existing S5 and S6 entries?
- What is the basis for the distinction between the 10% exemption cut-offs in S5 and S6 for aqueous and non-aqueous preparations, and is this distinction still warranted?
- Is there any need to adjust the current Schedule 5/Schedule 6 listing of iodocarb, or to review the current wording of the Schedule 5 and Schedule 6 entries? If so, what wording is suggested?

Substance details

The chemical appearance of 3-iodo-2-propynyl butyl carbamate[4] (iodocarb) is a white or slightly off white crystalline powder with a sharp pungent odour. It is highly soluble in organic solvents and moderately soluble in water.

Iodocarb has been reported uses such in cosmetic products (i.e. preservative in baby wipes) and as an approved constituent in pesticides by the Australian Pesticides and Veterinary Medicines Authority (APVMA).

Toxicity	Iodocarb	SPF[5] Classification
Oral LD_{50} (mg/kg bw)	1100-1795	Moderate to high
Dermal LD_{50} (mg/kg bw)	>2000	Low
Inhalational LC_{50} (mg/m^3/4 h)	6800	Low
Skin irritation	Irritant	
Eye irritation	Severe irritant	
Respiratory irritation	Irritant	
Skin sensitisation	Sensitiser	

Observations in humans

The chemical was found to be mildly irritating but not sensitising in clinical study done between 1998 and 2008 by the North American Contact Dermatitis Group (NACDG) using 0.1% iodocarb and/or 0.5% in petrolatum. For iodocarb-positive patients, the most frequent sites of dermatitis were scattered generalised distribution, hands, and arms. The majority (0.5%) of relevant reactions were due to personal care products (Warshaw et al., 2010).

In another clinical study, a 4% cosmetic formulation containing 0.0125% iodocarb was mildly irritating when applied under occlusive patches for 24 hours in a primary irritation study. Erythema without oedema was observed (Lanigan et al., 1998).

Significant irritation was not reported in 5- and 21-day cumulative irritation studies that tested 0.01 - 0.0125% iodocarb in formulation (Lanigan et al., 1998).

[4] NICNAS (2013): Inventory Multi-tiered Assessment and Prioritisation (IMAP). Human Health Tier II Assessment for Carbamic acid, butyl-, 3-iodo-2-propynyl ester. <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=80>

[5] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

There are several reports available on the sensitisation potential of iodocarb in humans. Recently, it has been described as an emerging contact allergen based on its increasing use in cosmetics (Davies and Johnston, 2011). Although the risk appears to be low at concentrations up to 0.1%, iodocarb - induced contact allergy may increase with increasing availability of iodocarb -containing cosmetic products or at higher concentrations or following longer term exposures (Badreshia and Marks, 2002 and Lanigan, 1998).

The recent available human data supports the findings from the animal studies that iodocarb is a skin sensitiser. Based on the positive results in the human patch tests and the positive animal studies, the chemical is recommended for classification with the risk phrase 'May cause sensitisation by skin contact' (Xi; R43).

Repeat dose toxicity

Based on the available information no hazard classification for repeat dose oral, dermal and inhalation toxicity is recommended, however a hazard classification for respiratory irritation is warranted.

Carcinogenicity

The chemical was not carcinogenic in rats and mice up to and including the highest dose levels (80 and 150 mg/kg bw/d) for rats and mice. In the mouse carcinogenicity study, an increased incidence of hepatocellular adenomas in high dose males (11/50) is not considered to be of biological relevance.

Based on the available study no hazard classification is recommended for carcinogenicity.

Reproductive and developmental toxicity

Overall the chemical is not considered a reproductive or developmental toxin. Based on the available data, no classification is recommended.

Neurotoxicity

Iodocarb was not neurotoxic when administered via the oral route. A NOEL of 300 mg/kg/day was noted based on decreases in locomotor activity (HSBD).

The absence of neurotoxic effects is supported by the repeat dose inhalation study and carcinogenicity studies which all investigated RBC and brain cholinesterase inhibition (ECHA, 2011).

Scheduling status

Schedule 5

3-IODO-2-PROPYNYL BUTYL CARBAMATE (Iodocarb) in preparations containing 10 per cent or less of 3-iodo-2-propynyl butyl carbamate **except** in aqueous preparations containing 10 per cent or less of 3-iodo-2-propynyl butyl carbamate.

Schedule 6

3-IODO-2-PROPYNYL BUTYL CARBAMATE (Iodocarb) **except**:

(a) when included in Schedule 5; or

(b) in aqueous preparations containing 10 per cent or less 3-iodo-2-propynyl butyl carbamate.

Scheduling history

In August 1988, the Drugs and Poisons Schedule Committee (DPSC) decided to include iodocarb in Schedule 5. The decision was based on the acute oral toxicity in rats (1470 mg/kg), acute dermal toxicity in rabbits (above 2000 mg/kg) and acute inhalational toxicity in rats (above 6890 mg/m^3).

In November 1988, the DPSC agreed to exempt from scheduling aqueous preparations containing 10 per cent or less iodocarb.

In June 2002, the NDPSC decided that the acute toxicity profile of iodocarb warranted inclusion in Schedule 6 with a cut-off to Schedule 5 for preparations containing 10 per cent or less and unscheduled for aqueous preparations containing 10 per cent or less.

Public pre-meeting submissions

One submission was received in support of clarifying the current restrictions on iodocarb. http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

ACCS advice to delegate

The Committee recommended amending the current Schedule 5 and 6 entries for 3-iodo-2-propynyl butyl carbamate to exempt cosmetic and personal care preparations containing 0.1 per cent or less of 3-iodo-2-propynyl butyl carbamate.

The Committee also recommended an implementation date of 1 February 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purpose for which a substance is to be used and the extent of use of a substance, and (f) any other matters that the Secretary considers necessary to protect public health of a substance.

The following reasons were noted:

- Low to moderate dermal toxicity in cosmetic and personal care preparations but also noting potential high inhalation toxicity in those products.
- Common preservative in domestically used products.
- Existing controls were considered adequate for other uses.
- Committee suggests that due to potential for high inhalation toxicity may warrant review at a later date.

Delegate's interim decision

The Delegate accepts the advice tendered by the ACCS and agrees to the proposed amendments to the S5 and S6 listings for 3-iodo-2-propynyl butyl carbamate (iodocarb).

An implementation date of 1 February 2014 is also agreed, since the proposed amendments would only affect cosmetic products containing more than 0.1% iodocarb, and the intent of the scheduling change is to restrict such use.

The Delegate notes, and accepts, ACCS advice that the listing of 3-iodo-2-propynyl butyl carbamate (iodocarb) in Appendix C for cosmetic use is not warranted, in that controls imposed via Schedule 5 & 6 listing should limit the use of this chemical in cosmetic products, and achieve appropriate label warnings (CAUTION or POISON signal heading) for any products formulated with this ingredient.

The Delegate also notes advice from a State jurisdictional source that the term 'personal care product' should be deleted from the schedule amendment because it is not defined in State/Territory legislation. This issue may require further advice from the ACCS.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* includes (b) purpose, (c) toxicity and (f) other matters that the Secretary considers necessary to protect public health of a substance:

- 3-iodo-2-propynyl butyl carbamate (iodocarb) is used as a preservative in a wide range of products and existing schedule entries adequately address these uses. The schedule amendments proposed here address the potential for adverse health effects (skin irritancy and inhalational toxicity) associated with its use in cosmetic and personal care products.
- At concentrations above 0.1% in products applied to the skin, there is a potential for irritancy and sensitisation. Cosmetic & personal care products intended for aerosolisation during use pose an inhalational irritancy/sensitisation risk.
- The intent of the scheduling amendments is to align controls over the use of 3-iodo-2-propynyl butyl carbamate (iodocarb) in cosmetic and personal care products with those imposed in US and Europe.

The delegate considered whether imposing restrictions on iodocarb in cosmetic and personal care products without the use of an Appendix C entry meets the NICNAS recommendations that controls be aligned with US (CIR) and European (SCCNFP) regulations. Application of S5/S6 controls does not 'ban' such uses, as achieved in the US and EU regulations, but the ACCS has supported S5/S6 scheduling as an appropriate level of control over use in cosmetics and personal care products.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (available at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=2);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[6]; and
- other relevant information.

Submissions on Interim Decision

One valid public submission was received, tentatively supporting the delegate's interim decision, asking the delegate to clarify the reasons for the Schedule 6 entry and the definition of "personal care". The submission also suggests that the wording of the cosmetic or personal care entry be amended to "*preparations containing greater than 0.1 per cent*".

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

[6] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

Delegates final decision

The delegate has considered the submission received following publication of the interim decision to the proposed amendments to the Schedule 5 and Schedule 6 listings for 3-iodo-2-propynyl butyl carbamate (iodocarb). The submission calls for clarification of the schedule amendments to clearly indicate that all types of cosmetic products containing more than 0.1% would be included in Schedule 6. The submission also requests that reference to 'personal care products' be deleted, in view of the fact that there is no definition of such products in the SUSMP and that the current NICNAS definition of 'cosmetics' adequately covers such products. On the basis of the submission the delegate has agreed to amend the proposed schedule 5 and 6 amendments accordingly.

The delegate accepts that the proposed schedule entries need clarification, in line with the submission received, and now proposes the following amended schedule entries:

SCHEDULE 5 – amendment

3-IODO-2-PROPYNYL BUTYL CARBAMATE (Iodocarb) in preparations containing 10 per cent or less of 3-iodo-2-propynyl butyl carbamate **except**:

(a) in aqueous preparations not for cosmetic use containing 10 per cent or less 3-iodo-2-propynyl butyl carbamate; or

(b) in cosmetic preparations (other than aerosolised preparations) containing 0.1 per cent or less of 3-iodo-2-propynyl butyl carbamate.

SCHEDULE 6 – amendment

3-IODO-2-PROPYNYL BUTYL CARBAMATE (Iodocarb) **except**:

(a) when included in Schedule 5;

(b) in aqueous preparations not for cosmetic use containing 10 per cent or less of 3-iodo-2-propynyl butyl carbamate (Iodocarb); or

(c) in cosmetic preparations (other than aerosolised preparations) containing 0.1 per cent or less of 3-iodo-2-propynyl butyl carbamate.

The delegate accepts that the 'reverse scheduling' wording used in the Schedule 5 and 6 exemption clauses to differentiate aqueous and non-aqueous preparations containing 10% or less 3-iodo-2-propynyl butyl carbamate (Iodocarb) is potentially confusing. However, there appears to be no other option to give effect to the decision to exclude all cosmetic products containing more than 0.1% 3-iodo-2-propynyl butyl carbamate (Iodocarb) from these exemptions and to include them, by default, in the primary listing in Schedule 6. It should also be clear that the words excluding aerosolised preparations from the exemption clauses, is to result in all aerosolised cosmetic preparations reverting to Schedule 6, irrespective of whether they contain less than 0.1% 3-iodo-2-propynyl butyl carbamate.

1.3 COCOYL GLYCINATE

Scheduling proposal

The NICNAS, under the New Chemicals Program, recommended the scheduling delegate consider including the following three salts of cocoyl glycinate in the SUSMP:

· glycine, N-coco acyl derivs., sodium salts;

· glycine, N-coco acyl derivs., potassium salts; and

- fatty acids, coco, reaction products with glycine, potassium salts.

The NICNAS indicated that these substances will be used as components of finished cosmetic rinse off and leave on products. Typical rinse-off products include cleansing products for skin and hair, whilst typical leave on products include skin lotions and creams.

The Chemicals Scheduling Delegate considered a proposal to include cocoyl glycinate in Schedule 6 with lower concentration cut-offs for leave-on and rinse-off preparations. This proposal also includes consideration of whether an Appendix E listing is required for cocoyl glycinate.

The delegate's reasons for referring this to the Advisory Committee on Chemicals Scheduling (ACCS) included:

- The ACCS has the necessary expertise to advice on the types of uses for which this industrial chemical warrants listing in the SUSMP and on the nature of controls to be applied through scheduling.

The delegate sought ACCS's advice on the following issues:

- Does the ACCS consider that the toxicological profile of cocoyl glycinate warrants inclusion in Schedule 6, as proposed, or in another schedule?
- What specific wording should be used for any schedule entry? Does the chemical name 'cocoyl glycinate' adequately cover the two specific salts (Na and K) addressed in the NICNAS evaluation report, AND the reaction product with coco fatty acids, glycine and potassium (CAS No. 1170699-63-2)?
- Does the ACCS support any cut-offs to a lower schedule, and if so, what wording gives effect to such exemption? Should there be different cut-offs for rinse-off and leave-on products, as proposed?
- Noting that the NICNAS evaluation specifically addresses a scheduling proposal for use of cocoyl glycinate in cosmetic and personal care products, can the ACCS advise whether there could be other uses that could be inadvertently captured by any listing in the SUSMP?
- To what extent does the current scheduling of related fatty acid esters such as lauryl and laureth sulfates, inform the appropriate scheduling of products containing cocoyl glycine? In particular, are the Appendix E statements for these two surfactants consistent with that proposed for cocoyl glycinate?

Substance details

Potassium cocoyl glycinate is the potassium salt of the amide formed from the reaction of coconut acid chloride and glycine. This substance is used as a hair conditioning agent and a surfactant-cleaning agent[7].

Sodium cocoyl glycinate is the sodium salt of the amide formed from the reaction of coconut acid chloride and glycine. This substance is used as a hair and skin conditioning agent, and a skin surfactant-cleaning agent[8].

[7] NICNAS (2010): Full Public Report File No: EX/130 (LTD/1306) - Glycine, N-coco acyl derivs., sodium salts (Sodium Cocoyl Glycinate) <http://www.nicnas.gov.au/__data/assets/word_doc/0008/6668/EX130FR.docx>

[8] Safety Assessment of Amino Acid Alkyl Amides as Used in Cosmetics. Cosmetic Ingredient Review. Available at http://www.cir-safety.org/sites/default/files/aaaamd022013slr.pdf

Toxicity	Substance 1a	Substance 1b	Substance 2	Substance 3
Oral toxicity (LD50 mg/kg bw)	>2000	>2000	>2000	>2000
Dermal toxicity (LD50 mg/kg bw)	Not provided	>2000**	Not provided	Not provided
Skin irritation	Slightly irritating at 5 per cent concentration	Moderately irritating	Irritating at 5 per cent concentration	Irritating at tested concentration (assumed to be up to 30 %)
Eye irritation	Irritating at 5 per cent concentration	Irritating	Irritating at 5 per cent concentration	Irritating at tested concentration
Skin sensitisation	No evidence of sensitisation at 5 per cent concentration	No evidence of sensitisation	No evidence of sensitisation up to 2.5 % concentration	No evidence of sensitisation up to 2.5 % concentration

Substance 1a = Glycine, N-coco acyl derivs., potassium salts (INCI name: Potassium Cocoyl Glycinate)
Substance 1b = Glycine, N-coco acyl derivs., sodium salts (INCI name: Sodium Cocoyl Glycinate)
Substance 2 = Glycine, N-coco acyl derivs., potassium salts (INCI name: Potassium Cocoyl Glycinate)
Substance 3 = Fatty acids, coco, reaction products with glycine, potassium salts (INCI name: Potassium Cocoyl Glycinate)

Irritation and sensitisation

Sodium cocoyl glycinate: The substance caused slight irritation to the skin of rabbits at 5 % concentration. The mean score achieved was 1.83, the substance therefore at 100 % is expected to have severe irritation effects. The NICNAS recommended that the substance should be classified at least as a skin irritant.

The substance caused slight irritation to the eyes of rabbits at 5 % concentration. Mild redness of the conjunctivae was persistent and was not reversible even after 7 days in 50 % of the animals tested (3/6 animals). The NICNAS recommended that considering the irritant effects observed at 5% concentration, the substance at higher concentrations should be classified as a severe eye irritant.

Hostapon (containing approximately 25 % of glycine, N-coco acyl derivs., sodium salts): 25 % of the substance was irritating to skin and eyes in tests conducted in rabbits. Irritation effects were also seen in dermal toxicity study at 68.5 %. The NICNAS indicated that the substance at 100 % concentration is expected to have severe eye irritation effects.

Potassium cocoyl glycinate: The substance caused moderate to severe erythema in the skin of rabbits at 5 % concentration. The symptoms have resolved after 1 week, however, all animals showed scaling by the end of the study period. The NICNAS noted that based on the persistence of skin scaling in all animals tested, the substance should be classified as irritating to the skin.

In an eye irritation study in rabbits, 5 % of the substance caused iridial inflammation, corneal opacity and signs of conjunctival irritation in all animals tested. Four out of 6 animals continued to show conjunctival redness at the end of the observation period. The NICNAS recommended that based on the persistence of conjunctival redness, the substance should be classified as a severe eye irritant.

Fatty acids, coco, reaction products with glycine, potassium salts: the substance caused slight irritation in the skin of rabbits at 5 % concentration. These symptoms had resolved within 1 week, though all the animals showed scaling at day 7. Considering this effect at the tested concentration, the substance at higher concentration should be classified as at least a skin irritant.

In an eye irritation study in rabbits, 5 % concentration of the substance caused iridial inflammation, corneal opacity and signs of conjunctival irritation in all animals tested. Four out of 6 animals continued to show conjunctival redness at the end of the observation period. The NICNAS recommended that based on the persistence of conjunctival redness, the substance is classified as a severe eye irritant.

Scheduling status

Neither cocoyl glycinate nor its salts are specifically scheduled.

Scheduling history

Neither cocoyl glycinate nor its salts have been considered for scheduling before.

Public pre-meeting submissions

One submission was received suggesting cocoyl glycinate could be included in Appendix B in the SUSMP, based on its extensive use in overseas markets without restriction and that its skin irritancy potential is lower than other similar surfactants. The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

ACCS advice to delegate

The ACCS recommended that a Schedule 6 entry for cosmetic and personal care preparations be created for cocoyl glycinate:

- for leave-on preparations containing more than 5 per cent of cocoyl glycinate
- for wash-off preparations containing more than 30 per cent of cocoyl glycinate

The ACCS recommended an implementation date of 1 February 2015.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee include; (a) the risks and benefits of the use of a substance, (b) the purpose for which a substance is to be used and the extent of use of a substance, (c) toxicity, and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The following reasons were noted:

- Risk of eye and skin irritation in cosmetic and personal care preparations.
- Effective surfactant agent with relatively lower toxicity.
- Wide personal use, but excluding non-cosmetic/personal care uses.
- Potentially severe eye and persistent skin irritation.
- Implementation date to take into account relabelling of imported products.

Delegate's interim decision

The Delegate accepts the advice tendered by the ACCS and agrees to include a new entry for cocoyl glycinate in Schedule 6, with exemptions as stated.

An implementation date of 1 February 2015 is also agreed, to allow sufficient time for any products affected by the scheduling decision to be re-labelled.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* includes: (b) purpose and (c) toxicity of a substance.

- All surfactants have the potential to cause irritation, particularly if left on the skin for prolonged periods or accidentally taken into the eye. Cocoyl glycinate, its salts and derivatives have somewhat reduced skin/eye irritancy potential, but warrant inclusion in Schedule 6 at high concentrations.
- The risk of adverse effects (particularly skin-eye irritancy) is sufficiently ameliorated at the cut-off concentrations proposed for exemption from the Schedule 6 entry.

The scheduling proposal referred in the NICNAS report specifically addressed the potential for skin-eye irritancy associated with the use cocoyl glycinate as a surfactant in cosmetic products (leave-on and rinse-off cleansers). Insufficient information was provided on possible use of cocoyl glycinate in other types of products available in the retail market that could also result in a significant exposure potential in the community. Therefore, the schedule entry and exemptions only apply to the use of cocoyl glycinate, its salts and derivatives in cosmetic products.

The ACCS recommendation suggests that a warning of potential eye irritation is not needed for products exempt from Schedule 6 scheduling, except for wash-off products containing between 5 and 30 per cent cocoyl glycinate. This is in contradiction of the recommendation in the NICNAS report, which suggests some potential for skin/eye irritancy associated with products at less than the proposed cut-offs. What is anomalous is that ACCS did not recommend any First Aid statements for products that would be covered by the provisions of Schedule 6 scheduling.

For consistency with other surfactant entries, the Delegate proposes to add an entry for cocoyl glycinate in Appendix E to cover scheduled products. The proposed entry in Appendix E is E1 - *If in eyes, wash out immediately with water*.

In making an interim decision, the Delegate accepts the implied advice of the ACCS that entries for cocoyl glycinate in Appendix F (warning statements and safety directions) are not needed, even for scheduled products. However, the Delegate welcomes comment on this matter during the consultation phase on this interim decision, and prior to making a final decision.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (available at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=2);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[9]; and
- other relevant information.

[9] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

Submissions on Interim Decision

One valid submission was received, asking the delegate to reconsider the mandatory label statement for wash-off preparations containing greater than 5% cocoyl glycinates. The submission cites that the warning statement does not provide useful first aid guidance, the cost involved in additional labelling for imported fully formulated and packaged products, and that the EU does not require such labelling. The submission also suggests removing the words "personal care".

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Delegates final decision

The delegate accepts that the proposed schedule entry needs amendment, in line with the submission received regarding the use of the words 'personal care', and now proposes the following schedule entry:

SCHEDULE 6 – New entry

COCOYL GLYCINATE in cosmetic preparations **except**:

(a) in leave-on preparations containing 5 per cent or less of cocoyl glycinate; or

(b) in wash-off preparations containing 30 per cent or less of cocoyl glycinate and, when containing more than 5 per cent of cocoyl glycinate labelled with a warning to the following effect:

If in eyes wash out immediately with water.

Appendix E, Part 2

POISON	STANDARD STATEMENT
Cocoyl glycinate	E1

1.4 DELTAMETHRIN

Scheduling proposal

The OCS recommended the scheduling delegate consider amending the Schedule 5 listings of deltamethrin to include ready-to-use mosquito nets containing 1 per cent or less deltamethrin.

The OCS has recommended that based on the estimated acute toxicity profile of the net, its physical presentation in polypropylene filaments and potential low level exposure to dislodgeable deltamethrin residues, a Schedule 5 listing for deltamethrin when impregnated in polypropylene net containing 1 per cent or less of deltamethrin is appropriate.

The Chemicals Scheduling Delegate considered a proposal to amend the Schedule 5 deltamethrin entry to include ready-to-use mosquito nets containing 1 per cent or less deltamethrin in Schedule 5 or to create a specific exemption for this product from current deltamethrin schedule entries.

The delegate has considered the OCS evaluation report and the recommendation to include ready-to-use mosquito nets containing 1 per cent or less deltamethrin in Schedule 5 or to create a specific exemption for this product from current deltamethrin schedule entries.

The delegate's reasons for referring this to the Advisory Committee on Chemicals Scheduling (ACCS) include:

- The history of the scheduling of deltamethrin and its preparations has been complex. While this is an apparently simple request by a sponsor to exempt mosquito nets (polypropylene net) containing up to 8.5 g/kg deltamethrin impregnated in a ready-to-use bed net, the Office of Chemicals Safety (OCS) evaluation report recommends listing in Schedule 5. The product sponsor has not provided any comment on this disparity at this stage. The delegate would therefore value advice from the ACCS on this scheduling submission.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support the OCS evaluation report recommendation for a specific entry in Schedule 5 for a ready-to-use mosquito nets containing up to 1 per cent deltamethrin?

- Alternatively, does the ACCS support unscheduling of this product?

- Please advise the specific wording to deltamethrin schedule entries to give effect to either of those options.

- Does the ACCS support the OCS report calculations of the likely exposures and the Margin of Exposure (MoE) estimates for adults and children?
  Please advise the specific wording to deltamethrin schedule entries to give effect to either of those options.

- If the recommendation is to support Schedule 5 listing, please comment on the feasibility of having Schedule 5 label warnings on a package that will presumably be discarded after opening and use of the net. Note that no Safety Directions or Warning Statements are proposed, but a Schedule 5 product would still need to carry the WARNING signal heading, and the prescribed First Aid Instructions.

Substance details

Deltamethrin is in the chemical class of pyrethroids and is effective against insects via ingestion and direct contact.

Pyrethroids are synthetic chemicals modelled after the pyrethrin components of pyrethrum. Unlike other pyrethroids, deltamethrin consists of one pure compound.

Pyrethroids, in general, interfere with normal production and conduction of nerve signals in the nervous system. Pyrethroids act on nerve membranes by delaying the closing of the activation gate for the sodium ion channel.

There are two classes of pyrethroids based on electrophysiological studies with nerves and symptoms of toxicity. Type II pyrethroids, including deltamethrin, have an α-cyano group that induces "long-lasting" inhibition of the sodium channel activation gate. This results in prolonged permeability of the nerve to sodium and produces a series of repetitive nerve signals in sensory organs, sensory nerves, and muscles. Deltamethrin and other Type II pyrethroids may also affect ion channels in the nervous system other than sodium channels, possibly due to their phosphorylation state.[10]

[10] Deltamethrin Technical Factsheet, National Pesticide Information Centre. Available at http://npic.orst.edu/factsheets/Deltatech.pdf

Toxicity	Deltamethrin	SPF[11] Classification	Mosquito net	SPF[12] Classification
Oral LD_{50} (mg/kg bw)	67 (rats) 19 (mice) 300 (dogs)	Moderate to high	>3952	Low
Dermal LD_{50} (mg/kg bw)	>2000	Low	>2000	Low
Inhalational LC_{50} (mg/m^3/4 h)	600	Moderate to high	N/D	
Skin irritation	Not irritant		Not irritant	
Eye irritation	Mild irritant		Not irritant	
Skin sensitisation	Not sensitiser		Not sensitiser	

*N/D = not determined

Scheduling status

Deltamethrin is listed in Schedules 5, 6 and 7.

Scheduling history

Decamethrin (also known as deltamethrin) was first considered at the February 1979 Poisons Schedule (Standing) Committee (PSSC) meeting. Based on the toxicology profile of decamethrin, the PSSC decided to list it in Schedule 6.

In May 1979, the PSSC reconsidered the decamethrin's Schedule 6 listing based on a submission requesting that decamethrin be reclassified into Schedule 7. This request was based on the findings that skin prickling and perspiration were observed in persons handling the substance and these symptoms persisted for a week. The PSSC decided to delete the Schedule 6 decamethrin entry and created a new Schedule 7 entry.

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

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

In February 2002, the National Drugs and Poisons Schedule Committee (NDPSC) considered the scheduling of a 25 per cent deltamethrin. The NDPSC agreed that, although the acute toxicity profile of the product was appropriate for a Schedule 5 entry, it remained concerned of the potential for neurotoxicity and the likely flow-on effects for other deltamethrin products. Accordingly, the NDPSC agreed that preparations containing 25 per cent or less should be captured in Schedule 6.

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

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

[11] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

[12] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

In February 2010, the NDPSC decided to exempt from scheduling for preparations containing ≤ 0.1 per cent deltamethrin from the requirements of scheduling.

In February 2012, the delegate based on the toxicity profile, decided that deltamethrin, when impregnated in plastic resin strip material containing 4 per cent or less of deltamethrin, be rescheduled from Schedule 7 to Schedule 5.

Public pre-meeting submissions

No public submissions were received.

ACCS advice to delegate

The Committee recommended that the Schedules 5 and 6 deltamethrin entries be amended to exempt from scheduling factory prepared mosquito nets containing 1 per cent or less of deltamethrin.

The ACCS recommended an implementation date of 1 February 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

- Benefit in reduction of vector borne disease.
- Formulation as an impregnated net reduces risk of toxicity.

Delegate's interim decision

The Delegate accepts the advice tendered by the ACCS meeting, and proposes that the deltamethrin entries in S5, S6 and S7 be amended to exempt factory-prepared mosquito nets containing 1 per cent or less deltamethrin.

The proposed wording of the schedule amendments is accepted.

The proposed implementation date of 1 February 2014 is agreed. This should enable sufficient time for the schedule amendment to be implemented before APVMA registration of the product.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* includes: (a) the risk and benefits, (c) toxicity and (d) dosage, formulation, labelling, packaging and presentation of a substance.

- Use of the product may have public health benefits through reduction of vector-borne diseases and the risks associated with such use are negligible.
- The low concentration of deltamethrin impregnated into the nets and the low potential for it to be dislodged during use suggest that exposure potential and toxicity risk is negligible and does not require control through scheduling.
- While an original package could have an attached label containing scheduling information (signal heading etc) if needed, such labels may not be practical for the unpacked product when in use. There is insufficient need for such warning labelling to warrant inclusion in a Schedule.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (not available);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[13]; and
- other relevant information.

Submissions on Interim Decision

No public submissions were received.

Delegates final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

SCHEDULE 5 – Amendment

DELTAMETHRIN:

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

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

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

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

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

except:

(a) in factory prepared mosquito nets containing 1 per cent or less deltamethrin; or

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

SCHEDULE 6 – Amendment

DELTAMETHRIN:

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

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

[13] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

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

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

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

except:

(a) when included in Schedule 5;

(b) in factory prepared mosquito nets containing 1 per cent or less of deltamethrin; or

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

SCHEDULE 7 – Amendment

DELTAMETHRIN: **except**

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

(b) in factory prepared mosquito nets containing 1 per cent or less of deltamethrin; or

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

1.5 ETHANOL, 2-(HEXYLOXY)- (HEXYLOXYETHANOL)

Scheduling proposal

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) process, recommended the scheduling delegate consider including the substance in Schedule 6.

The critical health effect of hexyloxyethanol is corrosivity, with delayed skin effects occurring post dose. This effect is consistent with the Schedule 6 of the Scheduling Policy Framework (SPF) factors. Although the current schedule listing for this chemical is correct, consideration should be given to creation of a new entry within Schedule 6 so that the associated Warning Statements can be better targeted to the corrosive effect.

The Chemicals Scheduling Delegate considered a proposal to create a separate Schedule 6 entry for hexyloxyethanol to complement the generic entry for ethylene glycol monoalkyl ethers. This consideration includes whether Appendices E, F and I entries are required for hexyloxyethanol.

The delegate considered a NICNAS proposal for a new schedule entry for hexyloxyethanol in Schedule 6.

The delegate's reasons for referring this to the Advisory Committee on Chemicals Scheduling (ACCS) include:

- This submission is relatively straightforward since it proposes a specific listing of hexyloxyethanol in Schedule 6, to complement the existing generic entry for ethylene glycol monoalkyl ethers. The primary purpose of the submission is to suggest more explicit Warning Statements to address the potential for corrosivity. The advice of the ACCS would be useful in making such amendments.

The delegate sought the following specific advice from the ACCS:

- Does the current scheduling of hexyloxyethanol in S6 remain appropriate and is there a need for a separate specific entry for hexyloxyethanol in S6 to complement the generic entry for ethylene glycol monoalkyl ethers?
- The current safety directions for the generic S6 entry are rather mild (1. *Avoid contact with eyes*; 4. *Avoid contact with skin*; 8. *Avoid breathing dust (or) vapour (or) spray mist*). Is there a case for stronger warnings against corrosivity when captured by the S6 entry – e.g., Warning Statement 2 *corrosive*
- Is there a need to also make separate entries for hexyloxyethanol in Appendices E (First Aid instructions) and I (Uniform paint standard), as well as in Appendix F (Warning Statements and safety directions)?
- Is the ACCS satisfied that products containing 10% or less hexyloxyethanol remain exempt from scheduling, and that no safety directions or Warning Statements would be applied?

Substance details

The chemical appearance of ethanol, 2-(hexyloxy)- (hexyloxyethanol)[14] is a water-white, odourless liquid.

Hexyloxyethanol has been reported in domestic uses (i.e. a range of cleaning products), commercial and site-limited uses (i.e. coalescing agent in latex paints and cleaners, colouring agent and in cleaning/washing agents).

Toxicity	Hexyloxyethanol	SPF[15] Classification
Oral LD_{50} (mg/kg bw)	738	Moderate to high
Dermal LD_{50} (mg/kg bw)	721	Moderate to high
Inhalational LC_{50} (ppm)	85	Moderate to high
Skin irritation	Corrosive potential	
Eye irritation	Corrosive potential	
Skin sensitisation	N/D	

Repeat dose toxicity

Based on the acute toxicity findings and repeat dose inhalation study, the chemical is not considered to be as potent a haemolytic agent as other monoethylene glycol ethers such as 2-butoxyethanol (CAS no 111-76-2).

Genotoxicity

In general, monoethylene glycol ethers are not genotoxic (OECD, 2006; NICNAS, 1996). The negative data available from several *in vitro* genotoxicity studies for the chemical supports this (OECD, 2006; REACH, 2011).

Carcinogenicity

There are no valid carcinogenicity studies available.

[14] NICNAS (2013): Inventory Multi-tiered Assessment and Prioritisation (IMAP). Human Health Tier II Assessment for Ethanol, 2-(hexyloxy)-. <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=83>

[15] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

Reproduction and developmental toxicity

No developmental effects were noted (even at concentrations that produced maternal toxicity) in rabbits and rats exposed to the chemical by inhalation (OECD, 2006).

Although certain short chain monoethylene glycol ethers such as 2-ethoxyethanol (110-80-5) are known reproductive toxicants, the ability of the glycol ethers to cause testicular toxicity decreases with increasing chain length (OECD, 2006). As 2-butoxyethanol (111-76-2), which has a shorter chain than the chemical, has been shown not to be a reproductive toxicant (OECD, 2006; NICNAS, 1996) the chemical is also considered not to be toxic to the reproductive system.

Scheduling status

Ethylene glycol monoalkyl ethers and their acetate are listed in Schedule 6 and Appendices E, F and I.

Schedule 6

ETHYLENE GLYCOL MONOALKYL ETHERS and their ACETATES, **except**:

(a) when separately specified in these Schedules; or

(b) in preparations containing 10 per cent or less of such substances.

Appendix E, Part 2

POISON	STANDARD STATEMENT
Ethylene glycol monoalkyl ethers and their acetates **except** when separately specified	A,G3,E2,S1

Appendix F, Part 3

POISON	WARNING STATEMENT	SAFETY DIRECTION
Ethylene glycol monoalkyl ethers and their acetates **except** when separately specified		1, 4, 8

Appendix I

The Second Schedule

SUBSTANCE	PROPORTION
Ethylene glycol monoalkyl ethers and their acetates **except** when separately specified	more than 10 per cent by vol

Scheduling history

In November 1984, the Poisons Schedule (Standing) Committee (PSC) considered scheduling of ethylene glycol monoalkyl ethers and their acetates. The PSC noted that ethylene glycol monomethyl- and monoethyl ethers were the most toxic of the series which demonstrated significant testicular effects, reproductive toxicity, haematological effects and were toxic at

inhalation levels at the TLV. The PSC also noted that other alkyl ethers of demonstrated haematological effects which increased with chain lengths. The PSC therefore decided to include preparations containing 5 per cent or more ethylene glycol monoalkyl ethers and their acetates in Schedule 6.

In February 1985, the PSC reconsidered the November 1984 decision and decided to raise the Schedule 6 ethylene glycol monoalkyl ethers and their acetates exemption cut-off from 5 per cent to 10 per cent.

Public pre-meeting submissions

One submission was received in support of the internationally aligned risk management of hexyloxyethanol. The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

ACCS advice to delegate

The Committee recommended that a new Schedule 6 entry be created specifically for hexyloxyethanol with a cut-off level for products containing 10 per cent of less of hexyloxyethanol remain exempt from scheduling. The Committee also supported that a new Appendix E and I entries be created specifically for hexyloxyethanol. Further, the Committee supported that an Appendix F entry be created specifically for hexyloxyethanol including a Warning Statement 2 Corrosive.

The ACCS recommended an implementation date of 1 February 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (c) the toxicity of a substance.

The following reasons were noted:

- Recognising that this substance has a different toxicity profile from the class entry ethylene glycol monoalkyl ethers.

Delegate's interim decision

The Delegate accepts the advice tendered by the ACCS meeting, and proposes that a new S6 entry be created for hexylethoxyethanol, to complement the generic entry for ethylene glycol monoalkyl ethers, with the same concentration cut-off for exemption from scheduling.

The proposed wording of the schedule amendments is accepted, including those for the new Appendix E, I and F entries,

The proposed implementation date of 1 February 2014 is agreed. There should be no implications for industry since the proposed schedule entries for hexylethoxyethanol mirror the existing generic entries for ethylene glycol monoalkyl ethers.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* includes: (c) the toxicity of a substance.

- While the toxicity profile of hexyloxyethanol is slightly different from that of the generic class entry for ethylene glycol monoalkyl ethers, it still fits with the criteria for S6 scheduling in the SPF.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the evaluation report (available at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=2);
- scheduling proposal;
- ACCS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[16]; and
- other relevant information.

Submissions on Interim Decision

No public submissions were received.

Delegates final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

SCHEDULE 6 – New entry

HEXYLOXYETHANOL **except** in preparations containing 10 per cent or less of hexyloxyethanol.

Appendix E, Part 2

POISON	STANDARD STATEMENT
Hexyloxyethanol	A,G3,E2,S1

Appendix F, Part 3

POISON	WARNING STATEMENT	SAFETY DIRECTION
Hexyloxyethanol	2	1, 4, 8

Appendix I

The Second Schedule

SUBSTANCE	PROPORTION
Hexyloxyethanol	more than 10 per cent by vol

[16] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

2. Scheduling proposals referred to the July 2013 meeting of the Advisory Committee on Medicines Scheduling (ACMS#9)

2.1 LORATADINE

Scheduling proposal

The medicines scheduling delegate considered a proposal to reschedule loratadine from Schedule 2 to unscheduled in oral preparations containing 10 mg or less in packs containing not more than 5 daily doses for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and over, with a warning labels recommending a daily dose not exceeding 10 mg loratadine for adults and children with body weight over 30 kg, or recommended daily dose not exceeding 5 mg loratadine for children with body weight 30 kg and under.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Substance details

Loratadine is a non-sedating, long-acting tricyclic antihistamine with selective peripheral H_1-receptor antagonistic activity. Once daily administration of loratadine provides effective treatment of allergic conditions including seasonal allergic rhinitis (SAR).

Scheduling status

Loratadine is currently listed in Schedules 2 and 4 and included under the entry Antihistamines in Appendix F.

Scheduling history

At the May 1992 National Drugs and Poisons Scheduling Committee (NDPSC) meeting, loratadine was first included in Schedule 4.

In November 1992, the NDPSC declined a proposal to reschedule loratadine from Schedule 4 to Schedule 3, on the grounds of an ADEC (now the Advisory Committee on Prescription Medicines – ACPM) recommendation and concerns about cardiac side effects.

In April 1994, the NDPSC rescheduled loratadine tablets to Schedule 3, and loratadine syrup to Schedule 3 in November 1995.

In May 1997, the NDPSC deferred a down-scheduling application for loratadine from Schedule 3 to Schedule 2, due to an article that was published in the Lancet, raising concerns about cardiovascular safety. At the August 1997 meeting, the NDPSC confirmed the Schedule 3 entry.

In February 1999, the NDPSC considered the rescheduling of loratadine from Schedule 3 to Schedule 2. The NDPSC also considered recommendations from the Trans-Tasman Harmonisation Working Party (TTHWP) in regard to non-sedating antihistamines. The NDPSC agreed that loratadine in preparations for oral use should be rescheduled, and that the restriction to 'only therapeutically active ingredient' should no longer apply. In November 1999, the NDPSC confirmed the down-scheduling of loratadine to Schedule 2.

After discussions in February 2012, the Schedule 2 and Schedule 4 entries were amended to exempt solid dose oral preparations containing 10 mg or less of loratadine in packs containing no more than 5 dosage units for the treatment of seasonal allergic rhinitis (SAR). The exemption was for treatment of adults and children over the age of 12 years.

Public pre-meeting submissions

Three public pre-meeting submissions were received. One supported the proposal, citing that the benefit to older children and adults would be justified.

The other 2 submissions did not support the proposal, recommending that no further changes be made to the current scheduling as the suggested amendment could adversely impact on the health of the age group.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

ACMS advice to the delegate

The ACMS recommended that current loratadine entries remain appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendation comprised the following:

- Risk of inappropriate use and delay in correct diagnosis.
- Lack of data on adverse effects/experiences/poisoning in Australia.
- No substantial public health benefit in exempting from schedules.
- Complicated dosage regimen with risk of inappropriate dosing.

Delegate's interim decision

The delegate has made an interim decision that the current scheduling of loratadine remains appropriate.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (a) the risks and benefits of the use of a substance; (b) the purposes for which the substance is to be used and the extent of use of the substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance and (f) any other matters that the Secretary considers necessary to protect public health.

The decision that the entry for loratadine remains appropriate included the following reasons:

- there is a risk of inappropriate use and delay in correct diagnosis;
- lack of data on adverse effects/experiences/poisoning in Australia;
- the proposed scheduling would have led to an unnecessarily complex requirement including reference to both age and right which differs from some overseas dosing. This would have led to a complicated dosage regimen with a risk of inappropriate dosing; and
- no substantial public health benefit in changing the scheduling and no evidence of any access issues for the current scheduling.

Submissions on interim decision

No submissions were received.

Delegates Consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[17];
- other relevant information.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

2.2 LURASIDONE

Scheduling proposal

The medicines scheduling delegate considered a proposal for a new Appendix K entry for lurasidone.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Substance details

Lurasidone hydrochloride is an atypical antipsychotic reported to be an antagonist at dopamine D_2, serotonin 5-HT_{2A} and 5-HT_7, and adrenergic α_{2A} and α_{2C} receptors, and a partial agonist at serotonin 5-HT_{1A} receptors. It may be given orally for the treatment of schizophrenia in an initial dose of 40 mg once daily with food; the maximum recommended daily dose is 80 mg. The dose should not exceed 40 mg daily in patients with moderate or severe hepatic or renal impairment.

Lurasidone hydrochloride is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and a daily dose of 40 mg should not be exceeded in those who are also taking moderate CYP3A4 inhibitors (such as diltiazem); use with potent CYP3A4 inhibitors (such as ketoconazole) or inducers (such as rifampicin) is not recommended.

Scheduling status

Lurasidone is not currently scheduled, but the delegate intends to include lurasidone in Schedule 4 (See Final Decisions on Matters not referred to an Expert Advisory Committee).

Scheduling history

As lurasidone is not currently scheduled, there is no scheduling history to report. However, lurasidone belongs to a class of substances considered as atypical antipsychotic agents. Other

[17] Scheduling Policy Framework for Medicines and Chemicals http://www.tga.gov.au/industry/scheduling-spf.htm

atypical antipsychotic agents, such as quetiapine and risperidone (among others) are included in Appendix K.

Public pre-meeting submissions

No public submissions were received for lurasidone.

ACMS advice to the delegate

The ACMS recommended that lurasidone be included in Appendix K of the Poisons Standard with an implementation date of 1 February 2014.

The matter under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the ACMS included (a) the risks and benefits of the use of the substance.

The recommendation comprised of the following:

- The risk of sedation warrants inclusion in Appendix K

Delegate's interim decision

The delegate has made an interim decision to list lurasidone in Appendix K.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (a) the risks and benefits of the use of a substance.

The decision to include lurasidone in Appendix K includes the following reasons:

- the risk of sedation is an issue with this group of drugs; and
- the risk of sedation warrants inclusion in Appendix K.

Submissions on interim decision

No submissions were received.

Delegates Consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[18];
- other relevant information.

[18] Scheduling Policy Framework for Medicines and Chemicals http://www.tga.gov.au/industry/scheduling-spf.htm

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

APPENDIX K – new entry

LURASIDONE

2.3 VORTIOXETINE HYDROBROMIDE

Scheduling proposal

The medicines scheduling delegate considered a proposal for a new Appendix L entry for vortioxetine hydrobromide.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Substance details

Substance details are not available.

Scheduling status

Vortioxetine hydrobromide is not currently scheduled, but the delegate intends to include vortioxetine in Schedule 4 (See Final Decisions on Matters not referred to an Expert Advisory Committee).

Scheduling history

At the May 1992 National Drugs and Poisons Scheduling Committee (NDPSC) meeting, loratadine was first included in Schedule 4.

As vortioxetine hydrobromide is not currently scheduled, there is no scheduling history to report. However, vortioxetine hydrobromide belongs to a class of substances considered as Selective Serotonin Reuptake Inhibitors (SSRIs). Other substances in this class, such as fluoxetine (among others) are already included in the SUSMP, but do not have Appendix L listings.

Public pre-meeting submissions

The ACMS noted that one public submission was received regarding the proposal; however no comment was given citing lack of information.

The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

ACMS advice to the delegate

The ACMS recommended to not list vortioxetine hydrobromide under Appendix L of the Poisons Standard.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the ACMS include (c) the toxicity of a substance.

The reason for the recommendation comprised of the following:

- Toxicity is not well established to warrant inclusion in Appendix L.

Delegate's interim decision

The delegate has made an interim decision that vortioxetine hydrobromine should not be listed in Appendix L.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (c) the toxicity of a substance.

The decision not to list vortioxetine hydrobromide in Appendix L included the following reasons:

- Lack of sufficient information to warrant inclusion in Appendix L. If vortioxetine hydrobromine was to be placed in Appendix L, then all SSRIs and SNRIs would need inclusion which would negatively affect pregnant women accessing antidepressant medication during pregnancy.
- Appendix L is reserved for highly teratogenic substances that women should not take during pregnancy and until such evidence is provided for these substances, vortioxetine and other SSRIs should not be listed in Appendix L.

Submissions on interim decision

No submissions were received.

Delegates Consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[19];
- other relevant information.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

[19] Scheduling Policy Framework for Medicines and Chemicals http://www.tga.gov.au/industry/scheduling-spf.htm

3. Scheduling proposals referred to the July 2013 joint meeting of the Advisory Committee on Chemicals Scheduling and Advisory Committee on Medicines Scheduling (ACCS-ACMS#6)

3.1 HYDROQUINONE AND MONOBENZONE

Scheduling proposal

The Chemicals and Medicines Scheduling Delegate (the Delegates) considered a considered a proposal to exempt from scheduling for gel nail preparation and dental bonding materials containing hydroquinone and monobenzone in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

The delegates' reasons for referring this proposal to the Advisory Committee on Chemicals Scheduling (ACCS) and Advisory Committee on Medicines Scheduling (ACMS) include:

- This is a re-scheduling request with a long history of concern by former scheduling committees about the safety of products containing hydroquinone and its more potent methyl ether (Monobenzone) in therapeutic and cosmetic products, especially when used for skin whitening. The current re-scheduling application warrants consideration by a joint meeting of the ACCS and ACMS.

The delegates sought the following specific advice from the ACCS and ACMS:

- Does the ACCS/ACMS agree that the risks associated with the use of hydroquinone and/or its methyl ethers as ingredients of nail hardening preparations are sufficiently slight that exemption of such products from the current Schedule 4 and Schedule 2 entries is warranted?

- If so, what wording is recommended to achieve this outcome in the current Schedule 4 and Schedule 2 entries?

- Noting that exemption from scheduling for nail hardening products would NOT exempt from the Warning statements for hydroquinone in Appendix F, but would exempt First Aid labelling requirements included in Appendix E, does the ACCS/ACMS recommend any changes to Appendix E or F entries?

- The NDPSC last reviewed toxicity concerns about hydroquinone in 2008 and 2009, introducing amendments that clarified the basis for exemptions for hair products containing less than 0.3 per cent, and reinforcing scheduling arrangements for external therapeutic and cosmetic products containing up to 2 per cent in Schedule 2, with all other therapeutic/cosmetic uses in Schedule 4. Has any new information become available since 2009 (e.g. the final USFDA rule) to support any change to current scheduling of hydroquinone?

- To what extent can the information on hydroquinone be used to support scheduling of its methyl ether (MEHQ)?

- Is there a need to clarify the Schedule 4 entries for monobenzone and hydroquinone? Monobenzone is the benzoyl ether of hydroquinone, and it was first included in Schedule 4 in 1969, with the current entry confirmed in 1987. The monobenzene entry currently lists monobenzone and other alkyl ethers of hydroquinone, even though monobenzone is NOT an alkyl ether. The hydroquinone Schedule 4 entry excludes alkyl ethers except where otherwise listed (e.g. in the monobenzone entry), so the submission is correct in stating that any concentration of the methyl ether (MEHQ) in a cosmetic preparation would be caught up in the Schedule 4 monobenzone listing. If specific exemptions are allowed from Schedule 4 for nail hardening preparations, does the monobenzone entry require parallel adjustment? Note that

there are currently no First Aid or Warning Statements prescribed for monobenzone in Appendices E and F.

Substance details

Hydroquinone (incl. its methyl ethers (MEHQ)) is a reducing agent that oxidizes to form quinone in air. It is used in nail polish products to inhibit premature polymerisation of methylacrylate-based liquid of a two component polymer system. It is also used in topical drugs as depigmenting agents for the skin and in hair preparations as lightening agent.

Monobenzone is the monobenzyl ether of hydroquinone, not an alkyl ether, although it is scheduled as 'monobenzone and other alkyl ethers of hydroquinone' in Schedule 4. Due to its chemical nature, it is used in a similar manner with hydroquinone (above).

In June 2002, Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers (SCCNFP) considered MEHQ in artificial nail system and noted that little toxicological data (no data on genotoxicity/mutagenicity) was provided for either hydroquinone or hydroquinone methyl ether. Assumptions are made but are not corroborated with data. The analytical data for the residual hydroquinone and hydroquinone methyl ether in the finished nail is inadequate.

The SCCNFP concluded that, due to the very low exposure to the consumer, the risk is minimal.

In 2006, based on data regarding potential carcinogenicity and reports of ochronosis, the USFDA proposed to reclassify these skin bleaching products (specifically containing hydroquinone) as drugs and make them available by prescription only.

The applicant has not provided toxicity data.

Scheduling status

Hydroquinone is listed in Schedules 2, 4 and 6 and Appendices E and F.

Monobenzone is listed in Schedule 4.

Hydroquinone salts or derivatives which are not alkyl ethers of hydroquinone are likely to be captured under the current hydroquinone entries through Paragraph 1(2)(c) of the SUSMP which indicates that "every salt, active principle or derivative of the substance, including esters and ethers, and every salt of such an active principle or derivative" will be captured by a schedule entry unless the contrary intention appears.

Scheduling history

Hydroquinone was first included in Schedule 4 in 1969 by the Poisons Schedule Sub-Committee (PSSC). This listing was due to concerns raised about the promotion and free availability of skin lightening creams which were being targeted to the PNG and Indigenous Australian populations.

In February 1971, the PSSC agreed to amend the Schedule 4 entry for hydroquinone to allow an exemption from scheduling for preparations of hydroquinone containing ≤ 2 per cent.

In May 1986, the Drugs and Poisons Schedule Committee (DPSC) considered deleting the ≤ 2 per cent exemption i.e. all human use hydroquinone and monobenzone becoming Schedule 4. The DPSC considered the overall Adverse Drug Reactions Advisory Committee (ADRAC) profile for hydroquinone and monobenzone and recommended that these substances warranted a Schedule 4 listing; however, this recommendation was not implemented.

In May 1987, the DPSC agreed to foreshadow creation of a new Schedule 2 entry for hydroquinone for human therapeutic or cosmetic use at ≤ 2 per cent (with an Appendix F warning statement). This was confirmed at the July 1987 Meeting.

In June 2008, the NDPSC, following a request from the Over the Counter (OTC) Medicines Section of the TGA, gave consideration as to whether hydroquinone was appropriately scheduled. The NDPSC noted concerns about possible carcinogenicity of hydroquinone with prolonged usage.

In October 2008, the NDPSC foreshadowed consideration of the rescheduling of hydroquinone and possible up-scheduling hydroquinone in preparations for human external use (excluding hair dyes) to Schedule 3.

Hair Preparations

In July 1987, the DPSC agreed to a general exemption from scheduling for ≤ 1 per cent hydroquinone in hair preparations.

In October 2008, the NDPSC noted that the European Union (EU) cut-offs for hydroquinone as an unapproved cosmetic ingredient (≤ 0.3 per cent in hair dyes) were more restrictive than the SUSMP controls (allowing ≤ 1 per cent).

In February 2009, the NDPSC considered a proposal to amend the exemption for use in hair dyes from 1 per cent to 0.3 per cent, in line with the European Union (EU) cut-offs. The NDPSC decided to amend the exemption for hair preparations containing hydroquinone from 1 per cent to 0.3 per cent or less.

Salts and Derivatives

In May 1987, the DPSC noted that monobenzone was actually more potent than hydroquinone and agreed to foreshadow that it should be in Schedule 4, together with other derivatives of hydroquinone for human therapeutic or cosmetic use, with no exceptions (whereas hydroquinone had a Schedule 2 entry). The NDPSC also noted that the other ether derivatives of hydroquinone were more potent than hydroquinone and had a similar side effect level to monobenzone.

In July 1987, the DPSC amended the foreshadowed monobenzone entry by specifying capture of 'other alkyl ethers of hydroquinone for human therapeutic use or cosmetic use' rather than all derivatives. [No reason was recorded]. This remains the wording in the current monobenzone entry.

In February and June 2009, the NDPSC considered the scheduling of hydroquinone for therapeutic and cosmetic use. Both meetings supported deferring a decision on the scheduling of hydroquinone in skin bleaching products (for external therapeutic use) until the USFDA report was available.

Public pre-meeting submission

One public submission was received. The submission supported the proposal as the use as a polymerisation inhibitor in nail polish posed minimal risk to human health once the substances are exposed to UV/LED light. The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions-1307.htm.

ACCS&ACMS advice to delegates

The joint Committee recommended that the Schedules 2 and 4 hydroquinone and Schedule 4 monobenzone entries be amended to exclude cosmetic nail preparations containing 0.02 per cent or less from scheduling.

The joint Committee recommends an implementation date of 1 February 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included; (a) the risks and benefits of the use of a substance, (b) the purpose, (c) the toxicity of a substance, (d) the dosage, formulation, labelling, packaging and presentation of a substance and (e) the potential for abuse.

- Risk is very low in cosmetic nail preparations because of the low concentration of hydroquinone and transient exposure.
- Benefits associated with proper use of cosmetic nail preparations.
- The purpose of the use of product is very specific.
- Toxicity is low in the product at that concentration and deactivation on exposure to light mitigates toxicity.
- No additional labelling is required.
- Minimal potential risk.

Delegates' interim decision

The Delegates accept the advice of the Joint ACCS/ACMS meeting, that cosmetic nail preparations containing 0.02% or less of hydroquinone, methylhydroquinone or monobenzone should be exempted from the current entries in Schedules 2 and 4.

The proposed amendments to the current schedule entries recommended by the Committees are accepted.

The delegates considered the relevant matters under section 52E (1) of the Therapeutic Goods Act 1989 includes: (a) the risks and benefits, (b) purpose, (c) toxicity of a substance.

- Risk is very low in cosmetic nail preparations because of the low concentration of these polymerisation agents and the transient nature of their potential exposure.
- This specific scheduling exemption relates only to use of these materials at low concentration in light-activated cosmetic nail preparations.
- Toxicity at such a low concentration in the products is expected to be minimal and the concentration of the materials, and hence the toxicity, is expected to be further mitigated by deactivation on exposure to light.

It is noted that hydroquinone and methylhydroquinone may also be used in light-activated dental bonding materials. However a specific schedule exemption in Schedules 2 & 4 for such use is not required because of the general exemption for medical/veterinary adhesives, glues and cements in Appendix A.

Submissions on interim decision

One valid submission was supporting the interim decision. The submission asks for the implementation date to be brought forward to allow to benefit businesses who wish to sell these products. The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Delegates' consideration

The delegate considered the following in regards to this proposal:

- scheduling application (not publically available);
- ACCS & ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;

- scheduling factors[20]; and
- other relevant information.

Delegate's final decision

The delegate has reviewed the public submissions and other evidence and has confirmed the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The ACCORD proposal to bring forward the implementation date of 1 Feb 2014 is not accepted. The date of publication of the SUSMP Amendment is the formal trigger for the States/Territories to amend their poisons lists, and this publication date cannot be brought forward. The issue of monitoring compliance with poisons legislation rests with the States and Territories.

Schedule entry

Schedule 2 - Amendment

HYDROQUINONE (excluding monobenzone and alkyl ethers of hydroquinone included in Schedule 4) in preparations for human external therapeutic or cosmetic use containing 2 per cent or less of hydroquinone **except:**

(a) In hair preparations containing 0.3 per cent or less of hydroquinone; or

(b) in cosmetic nail preparations containing 0.02 per cent or less of hydroquinone.

Schedule 4 - Amendment

HYDROQUINONE (other than its alkyl ethers separately specified in this Schedule) in preparations for human therapeutic or cosmetic use **except**:

(a) when included in Schedule 2; or

(b) in hair preparations containing 0.3 per cent or less of hydroquinone; or

(c) in cosmetic nail preparations containing 0.02 per cent or less of hydroquinone.

Schedule 4 – Amendment

MONOBENZONE and alkyl ethers of hydroquinone for human therapeutic use or cosmetic use **except** in cosmetic nail preparations containing 0.02 per cent or less of monobenzone or alkyl ethers of hydroquinone.

3.2 PRADOFLOXACIN

Scheduling proposal

The Chemicals Scheduling Delegate and the Medicines Scheduling Delegate (the delegates) considered a proposal to include pradofloxacin in Schedule 4 or Schedule 7. This proposal also includes if a Schedule 4 listing is appropriate for pradofloxacin, whether this entry should specify 'for the treatment of animals'.

The delegates sought the following specific advice from the Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS):

[20] Scheduling Policy Framework for Medicines and Chemicals (2010) <http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf>

- Does the ACCS/ACMS support listing of pradofloxacin in Schedule 4 on the basis that veterinarian supervision of treatment is required?
- If so, should the listing in Schedule 4 be restricted to 'animal use only'?
- Does the ACCS/ACMS agree that toxicological issues (genotoxicity and developmental toxicity) raised in the 2006 evaluation have been adequately addressed in the current evaluation report, and in the European Medicines Agency (EMA) report?
- If not, does the ACCS/ACMS consider that a more restrictive schedule (e.g. S7) would be more appropriate for pradofloxacin?
- Although no longer a matter for scheduling consideration, does the ACCS/ACMS have any opinion on the adequacy of the First Aid Instructions & Safety Directions, and would it advise the OCS to incorporate them into the FAISD handbook?

Substance details

Pradofloxacin, a fifth generation fluoroquinolone, is a new veterinary 8-cyano-fluoroquinolone developed for use against bacterial infections in dogs and cats involving both aerobic and anaerobic bacteria[21].

The primary mode of action of the fluoroquinolones involves interaction with enzymes essential for major DNA functions such as replication, transcription and recombination. The primary targets for pradofloxacin are the bacterial DNA gyrase and topoisomerase IV enzymes. Reversible association between pradofloxacin and DNA gyrase, or DNA topoisomerase IV in the target bacteria results in inhibition of these enzymes and rapid death of the bacterial cell. The rapidity and extent of bacterial killing are directly proportional to the drug concentration[22].

Toxicity

Pradofloxacin showed low acute oral toxicity in mice and rats. It has a low acute dermal toxicity in rats and it was not a skin irritant in rabbits or a skin sensitiser in guinea pigs. Eye irritation potential in a rabbit study was adjudged to be slight. In a study in guinea pigs, an oral dose of pradofloxacin was stated to cause slight photoirritation of the skin.

The antibiotic activity of pradofloxacin was responsible for a number of adverse findings which were reversible. These include diarrhoea and altered faecal excretion, increased water intake, caecal dilation and intestinal pathology which were probably secondary to local microbiological effects on colonic microflora. Suppression of the resident microbial population and the subsequent reduced stimulation of the immune system was the likely cause of decreased leukocyte counts and thymus weight, and altered pathology in the lymph nodes. While these effects are not considered to arise from a toxicological mechanism they are nonetheless treatment-related and unwanted.

In dogs, pradofloxacin exposure was associated with degenerative changes of the articular cartilage in multiple joints consisting of blisters or erosions, proliferative clusters of chondrocytes and inflammation of the synovial membrane. Arthropathy is a well-known property of the fluoroquinolone antibiotics and was observed after single and repeated doses in dogs. Degeneration of knee joint cartilage was also found in a single study in rats given repeat doses of pradofloxacin.

[21] Peter Silly et al, Bactericidal properties of pradofloxacin against veterinary pathogens, Veterinary Microbiology Volume 157, Issues 1-2. 25 May 2012.
[22] Annexe 1, Summary of Product Characteristics, http://ec.europa.eu/health/documents/community-register/2012/20120910124289/anx_124289_en.pdf

Tubular degeneration/regeneration and altered staining and swelling of renal tubular epithelial cells in rats and enlarged and pleomorphic nuclei in the tubular epithelium of the renal cortex in mice were detected at high single or multiple doses. Since 30 to 40 per cent of an oral dose of pradofloxacin was eliminated in the urine of rats, kidney tissue would be exposed to high concentrations of pradofloxacin which could account for the kidney as a target tissue for toxicity.

Chronic toxicity/carcinogenicity studies in rats revealed increased bile duct hyperplasia and periportal infiltration in the liver after 1 year of treatment. The incidence of bile duct hyperplasia was similar to controls at 2 years indicating that treatment may have hastened the onset. In rats, approximately 20 per cent of an oral dose of pradofloxacin was excreted via the bile into the faeces. The resulting prolonged exposure of the biliary system to high concentrations of drug could provide the conditions for stimulation of increased epithelial cell division. There was no evidence of neoplastic activity in rats.

Products

No data was submitted on the toxicity of the tablet formulations. The formulations are of different strengths but the concentration of ingredients in each is the same. Therefore, the acute toxicity estimates were based on the available information on the active and excipient components and their concentration in the formulation.

The applicant has proposed that the tablet formulations will be available in blister packs and the suspension formulation will be packaged in high density bottles with a child resistant closure. These measures would limit the likelihood of access by children. Similarly, the label statements required for a Schedule 4 substance will indicate the need to keep the products out of the reach of children. In addition, a label statement indicating the products are harmful if swallowed would be appropriate.

Scheduling status

Pradofloxacin is not specifically scheduled.

Other fluoroquinolones, such as ciprofloxacin, difloxacin, enrofloxacin, marbofloxacin and orbifloxacin are listed in Schedule 4.

Scheduling history

Pradofloxacin has not been considered previously.

Public pre-meeting submissions

No public submissions were received.

ACCS&ACMS advice to delegates

The joint Committee recommended that preparations containing pradofloxacin be included in Schedule 4.

The joint Committee also recommended an implementation date of 1 February 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (b) the toxicity.

The following reason was noted:

- Antibiotics require oversight of an appropriate prescriber.

Delegates' interim decision

The Delegates accept the advice tendered by the Joint ACCS/ACMS meeting, and propose that pradofloxacin be included in Schedule 4.

The proposed entry in Schedule 4 is:

PRADOFLOXACIN

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* includes: (b) the purposes for which a substance is to be used and the extent of use of a substance.

- Pradofloxacin is an antibiotic and its use requires the oversight of an appropriate prescriber.

Submissions on interim decision

No submissions were received.

Delegates Consideration

The delegate considered the following in regards to this proposal:

- scheduling proposal;
- public submissions received;
- the evaluation report (not publicly available);
- ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[23];
- other relevant information.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

Schedule 4 – New entry

PRADOFLOXACIN.

[23] Scheduling Policy Framework for Medicines and Chemicals http://www.tga.gov.au/industry/scheduling-spf.htm

Part B - Final decisions on matters not referred to an expert advisory committee

4. Chemicals

4.1 TYLOSIN

Scheduling Proposal

The Chemicals Scheduling Delegate and the Medicines Scheduling Delegate (the delegates) considered a proposal to reschedule tylosin from Schedule 5 to Schedule 4 in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

This matter was referred to the joint ACCS & ACMS meetings held in June 2012 and March 2013. Based on the Committee's advice and available information the delegates decided to defer making any schedule change, pending receipt of further information.

Scheduling Status

Tylosin is listed in Schedules 4 and 5.

Tylosin is a macrolide antimicrobial agent approved in Australia by the APVMA for use in poultry, pigs and cattle. As of March 2013, tylosin has been available as an injection, water-soluble antimicrobial preparation and as premix. While injectable and water-soluble formulations are in Schedule 4 (Prescription Animal Remedy), the feed premix formulations are, according to the concentration of tylosin in the marketed premix, either in Schedule 4 or in Schedule 5 (available over-the-counter without a prescription).

Scheduling History

In November 1968, the then Poisons Schedule Sub-Committee (PSSC) recommended that an entry group 'antibiotics' be included in Schedule 4 except when tylosin and other macrolides bacitracin, erythromycin and oleandomycin when added to animal feedstuffs for the purpose of growth promotion in concentrations not exceeding 50 ppm, which should be exempt from scheduling. Antibiotic premixes for growth promotion purposes containing the antibiotics above in concentrations greater than 50 ppm but not in excess of 20,000 ppm should be exempt from Schedule 4 when packed and labelled in accordance with Schedule 6 of the Uniform Poisons Schedules. Water soluble antibiotic preparations intended for addition to animals' drinking water should not be made available without prescription.

In May 1977, the then Poisons Schedule Committee (PSC) decided to amend the Schedule 4 entry for antibiotics to include animal feedstuffs containing bacitracin, erythromycin, oleandomycin, tylosin and virginiamycin in concentration of 50 ppm or less of the total active antibiotic principles. The PSC was of the opinion that the continued use of antibiotics as growth promotions in animal feedstuffs could lead to an impairment of their efficacy in the treatment of human disease.

In May 1978 specific entries for antibiotics including tylosin, bacitracin, erythromycin, oleandomycin and virginiamycin were included in Schedule 4, except in animal feedstuffs for growth promotion in concentrations of 50 mg / kg or less of the total active antibiotic principle (remained Schedule 6).

In November 1986, the then Drugs and Poisons Schedule Standing Committee (DPSSC) considered a submission to remove tylosin from Schedule 4 to Schedule 6. The review noted that if the concentration of tylosin in the premix was increased it would increase the chance of erythromycin resistance occurring in possible human pathogens. The DPSSC decided not to remove the Schedule

4 entry and recommended the Schedule 6 level of tylosin in premixes be increased from 2 to 5 per cent.

In November 1990, the DPSC considered an apparent anomaly in the scheduling of tylosin. The DPSC confirmed the current scheduling that the Schedule 4 entry related to uses involving therapeutic claims while Schedule 6 entry was solely for growth promotion purposes.

In May 1993, the DPSC decided to include safety directions for a Schedule 6 tylosin stockfeed premix.

In February 1996, the National Drugs and Poisons Schedule Committee (NDPSC) decided to reschedule tylosin from Schedule 6 to Schedule 5. The NDPSC considered that the registered products for oral use fell within the acute oral criteria of the new draft guidelines for Schedule 5 and recommended that tylosin when in veterinary products for oral use should be classified as Schedule 5.

In 1999, the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) recommended "that all antibiotics for use in humans and animals (including fish) be classified as Schedule 4 (prescription only)." The JETACAR report also recommended that a review of the macrolides (tylosin, kitasamycin, oleandomycin) be undertaken as a priority to assess efficacy and to ensure that continued use is "not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms."

In February 2003, the NDPSC scheduled / rescheduled all antibiotics (except tylosin, kitasamycin, oleandomycin) for use in human and animals in Schedule 4: viginiamycin, bacitracin, cuprimyxin, erythromycin, hygromycin, nalidixic acid, nisin, spiramycin and avoparcin as part of its response to the recommendations (in 1999) of the JETACAR

The October 2003 NDPSC meeting considered a letter sent to feed mill sales representatives from XXXXX in which the company highlighted the Committee's decision regarding the rescheduling of virginiamycin to Schedule 4. XXXXX letter mentioned that XXXXX (containing tylosin) remained in Schedule 5 and was unaffected by the NDPSC decision. The NDPSC agreed to refer claims of inappropriate promotion of antibiotics that are yet to be reviewed under JETACAR to Expert Advisory Group on Antimicrobial Resistance (EAGAR) and the APVMA.

In June 2012, the joint Committee considered a referral from the medicines and chemicals scheduling delegates to consolidate the scheduling of all uses of tylosin in Schedule 4. The joint Committee agreed that they were unable to provide the scheduling delegates informed advice at that stage. The delegates noted that the APVMA review on macrolides was yet to be completed. The delegates therefore decided not to make a scheduling decision on this issue and referred this matter to the March 2013 joint Committee meeting for advice.

Public Pre-Meeting Submissions

Not applicable.

ACCS & ACMS Advice to the Delegate – March 2013 Meeting

The ACCS & ACMS considered the referral from the scheduling delegates to reschedule tylosin from Schedule 5 to Schedule 4 in the Standard for the Uniform Scheduling of Medicines and Poisons. The Committees advised the delegates that it was unable to make a scheduling recommendation or to provide advice at this time due to lack of provision to the Committees of all of the available data in the form of the macrolide review or an alternative acceptable process.

Delegates' Interim Decision – June 2013

The delegates decided to defer making an interim decision on the consolidation of the scheduling of tylosin in to Schedule 4, pending receipt of further advice on the key issue of the risks of expanding antibiotic resistance associated with its use as an animal health feed additive (the current Schedule 5 and exempt uses).

Submissions on Interim Decision

A submission was received from a sponsor of a product containing tylosin and was considered by the delegates in making a scheduling decision. The redacted public submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Delegates' Consideration

The delegates considered the following in regards to this proposal:

- evaluation report (not publically available);
- scheduling proposal;
- ACCS & ACMS advice;
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[24];
- public submissions (pre- and post-meeting); and
- other relevant information.

Delegates' Final Decision

The delegates have reconsidered this matter and decided to delete the current entry for tylosin in Schedule 5 with an implementation date of 1 June 2014.

The relevant matters considered by the delegate under section 52E (1) of the *Therapeutic Goods Act 1989* includes (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance and (f) any other matters that the Secretary considers necessary to protect public health.

The decision to revert all uses of tylosin to Schedule 4 incorporated the following reasons:

- The scheduling decision addresses an anomaly that has existed since 2003, when the then NDPSC responded to Recommendation 6 of the JETACAR report and re-scheduled animal treatment antibiotics to Schedule 4.
- At that time, consideration of the re-scheduling of animal feed pre-mixes containing up to 5% tylosin was deferred pending a review of macrolide antibiotic use in animal treatment.
- This review has not been completed, but the delegates have sought expert advice on the potential for veterinary use of tylosin to contribute to antibiotic resistance development (a key issue in the JETACAR report). This input has included advice from the APVMA, joint meetings of the ACCS &ACMS, the sponsor of an affected product, and independent expert on antibiotic resistance, who was also a previous member of the JETACAR panel.

[24] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

- The decision to delete the current Schedule 5 entry for tylosin and the other exemptions in the current Schedule 4 entry is to finalise Recommendation 6 of the JETACAR report and to align tylosin scheduling with that of other antibiotics used in animal treatment to require veterinary prescription of their use.

Schedule Entry

Schedule 4 – Amendment

TYLOSIN. ~~**except:**~~

~~**(a)** when included in Schedule 5;~~

~~**(b)** in animal feeds containing 50 mg/kg or less of antibiotic substances:~~

~~(i) for growth promotion;~~

~~(ii) for the prevention of liver abscesses in cattle; or~~

~~(iii) for the prevention of ileitis in pigs; or~~

~~**(c)** in milk replacers for calves, or starter rations for pigs, containing 100 mg/kg or less of antibiotic substances.~~

Schedule 5 – Delete entry

~~TYLOSIN in animal feed premixes containing 5 per cent or less of antibiotic substances:~~
~~(a) for growth promotion;~~

~~(b) for the prevention of liver abscesses in cattle; or~~

~~(c) for the prevention of ileitis in pigs.~~

5. New chemical entities – medicines for human therapeutic use

5.1 AFATINIB DIMALEATE

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of afatinib dimaleate a new chemical entity for a human therapeutic medicine.

Afatinib dimaleate is a tyrosine kinase inhibitor (TKI) that irreversibly inhibits human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR) kinases. The proposed indication is:

GIOTRIF® is indicated as monotherapy for treatment of patients with metastatic adenocarcinoma of the lung whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or L858R substitution mutations. In patients previously treated with EGFR tyrosine kinase inhibitors, GIOTRIF should only be used if clinical benefit was sustained for 12 or more weeks on such therapy

The indication approved at registration may differ from this.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Afatinib dimaleate is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Afatinib dimaleate is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include afatinib dimaleate in Schedule 4, with an implementation date of 1 Feb 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use and (c) toxicity, d) dosage, formulation, labelling, packaging and presentation, and (e) the potential for abuse of afatinib dimaleate.

The delegate decided that the reasons for the final decision comprise of the following.

- Afatinib dimaleate is a new chemical entity with no marketing experience in Australia.
- The proposed indication is: GIOTRIF® is indicated as monotherapy for treatment of patients with metastatic adenocarcinoma of the lung whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or L858R substitution mutations. In patients previously treated with EGFR tyrosine kinase inhibitors, GIOTRIF should only be used if clinical benefit was sustained for 12 or more weeks on such therapy
- Toxicity has been taken into account in consideration of benefit- risk.
- The aspects of dosage, formulation, labelling, packaging and presentation have been evaluated and found acceptable in the TGA evaluation process.
- The potential for abuse of this substance is limited.

Schedule entry

Schedule 4 – New Entry

AFATINIB DIMALEATE.

5.2 DABRAFENIB MESILATE

Scheduling proposal

For the delegate to consider the scheduling of the new chemical entity **dabrafenib mesilate.**

Dabrafenib mesilate is an antineoplastic agent that inhibits BRAF kinase. It selectively binds to and inhibits the activity of B-raf (BRAF), which may inhibit the proliferation of tumor cells which contain a mutated BRAF gene. B-raf belongs to the raf family of serine/threonine protein kinases and plays a role in regulating the MAP kinase/ERKs signaling pathway, which may be constitutively activated due to BRAF gene mutations.

Dabrafenib mesilate is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

- Dabrafenib mesilate is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).
- Dabrafenib mesilate is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the Therapeutic Goods Act 1989.
- The Scheduling Policy Framework scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include dabrafenib mesilate in Schedule 4, with an implementation date of 1 Feb 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use and (c) toxicity, d) dosage, formulation, labelling, packaging and presentation, and (e) the potential for abuse of dabrafenib mesilate.

The delegate decided that the reasons for the final decision comprise of the following.

- Dabrafenib mesilate is a new chemical entity with no marketing experience in Australia.
- During the TGA evaluation process, the benefits have been found to outweigh the risks of use in the indicated population.
- The indication is: treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.
- Toxicity has been taken into account in consideration of benefit – risk.
- The aspects of dosage, formulation, labelling, packaging and presentation have been evaluated and found acceptable in the TGA evaluation process.

· The potential for abuse of this substance is limited.

Schedule entry

Schedule 4 – New Entry

DABRAFENIB MESILATE.

5.3 DOLUTEGRAVIR

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of dolutegravir, a new chemical entity for a human therapeutic medicine.

Dolutegravir is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 12 years of age.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Dolutegravir is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Dolutegravir is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

· The TGA evaluation report.

· The advice of the Advisory Committee on Prescription Medicines.

· Subsection 52E(1) of the *Therapeutic Goods Act 1989*.

· The Scheduling Policy Framework scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include xxxxx in Schedule 4, with an implementation date of 1 Feb 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use and (c) toxicity, d) dosage, formulation, labelling, packaging and presentation, and (e) the potential for abuse of dolutegravir.

The delegate decided that the reasons for the final decision comprise of the following.

· Tivicay is a new chemical entity with no clinical experience in Australia.

· TIVICAY is to be used for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 12 years of age.

- Many toxic effects are associated with the use of this class of drug, such as Hypersensitivity reactions, Immune Reconstitution Syndrome
- There is also possible interaction with other drugs.
- TIVICAY are tablets to be taken orally
- Not aware of any potential for abuse

Schedule entry

Schedule 4 – New Entry

DOLUTEGRAVIR.

5.4 MIRABEGRON

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of mirabegron, a new chemical entity for a human therapeutic medicine.

Mirabegron is a beta3-adrenoceptor agonist which increases bladder capacity by relaxing the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle. It is indicated for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Mirabegron is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Mirabegron is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice on the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include mirabegron in Schedule 4, with an implementation date of 1 Feb 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use and (c) toxicity, d) dosage, formulation, labelling, packaging and presentation, and (e) the potential for abuse of mirabegron.

The delegate decided that the reasons for the final decision comprise of the following.

- It is a new chemical entity with no clinical/marketing experience in Australia.
- Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome.
- Suitable for Schedule 4
- Once daily, oral treatment, 25 mg or 50 mg, as prolonged-release film-coated tablets, which are packed in blisters in cartons
- Does not appear to produce dependence

Schedule entry

Schedule 4 – New Entry

MIRABEGRON.

5.5 OCRIPLASMIN

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of ocriplasmin, a new chemical entity for a human therapeutic medicine.

Ocriplasmin is recombinant truncated form of human plasmin produced by recombinant DNA technology in a Pichia pastoris expression system. The finished drug product is a sterile, clear solution in a single-use glass vial containing 0.5 mg ocriplasmin in 0.2 mL fill volume to be diluted with an equal volume of 0.9% sodium chloride prior to use and is intended for intravitreal administration.

Ocriplasmin is proposed for "the treatment of symptomatic vitreomacular adhesion (sVMA) including those associated with macular hole in adults".

The delegate decided to make a delegate-only decision to include ocriplasmin in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Ocriplasmin is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons*.

Ocriplasmin is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling:

- The new drug application.
- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include ocriplasmin in Schedule 4, with an implementation date of 1 September 2013.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits of ocriplasmin.

The delegate decided that the reasons for the final decision comprise of the following.

- It is a new chemical entity with no [clinical/marketing] experience in Australia.

Schedule entry

Schedule 4 – New Entry

OCRIPLASMIN.

5.6 ROMIDEPSIN

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of romidepsin, a new chemical entity for a human therapeutic medicine.

Romidepsin is an antineoplastic agent indicated for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior systemic therapy.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

- Romidepsin is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).
- Romidepsin is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include romidepsin in Schedule 4, with an implementation date of 1 Feb 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use and (c) toxicity, d) dosage, formulation, labelling, packaging and presentation, and (e) the potential for abuse of romidepsin.

The delegate decided that the reasons for the final decision comprise of the following.

- romidepsin is a new chemical entity with no marketing experience in Australia.
- During the TGA evaluation process, the benefits have been found to outweigh the risks of use in the indicated population.
- Romidepsin is indicated for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior systemic therapy.
- Toxicity has been taken into account in consideration of benefit – risk.
- The aspects of dosage, formulation, labelling, packaging and presentation have been evaluated and found acceptable in the TGA evaluation process.
- The potential for abuse of this substance is limited.

Schedule entry

Schedule 4 – New Entry

ROMIDEPSIN

5.7 TRAMETINIB DIMETHYL SULFOXIDE

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of trametinib dimethyl sulfoxide, a new chemical entity for a human therapeutic medicine.

Trametinib dimethyl sulfoxide is a reversible allosteric inhibitor of MEK1 and MEK2 (mitogen-activated extracellular signal regulated kinases 1 and 2).

The sponsor's proposed indications for use of trametinib dimethyl sulfoxide are as follows:

MEKINIST as a monotherapy and in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable or metastatic (Stage IV) melanoma.

MEKINIST as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy.

These indications are subject to review / potential modification prior to inclusion of trametinib dimethyl sulfoxide in the ARTG.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Trametinib dimethyl sulfoxide is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

It is noted that the proposed formulation is a solvate using a relatively small amount of dimethyl sulfoxide (DMSO), which is included in the SUSMP in Schedule 4 when intended for therapeutic use. DMSO is considered an excipient in the context of trametinib dimethyl sulfoxide.

Trametinib dimethyl sulfoxide is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include trametinib dimethyl sulfoxide in Schedule 4, with an implementation date of 1 Feb 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use and (c) toxicity, d) dosage, formulation, labelling, packaging and presentation, and (e) the potential for abuse of trametinib dimethyl sulfoxide.

The delegate decided that the reasons for the final decision comprise of the following.

- Trametinib dimethyl sulfoxide is a new chemical entity with no marketing experience in Australia.
- Its proposed indication is: MEKINIST as a monotherapy and in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable or metastatic (Stage IV) melanoma.MEKINIST as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see CLINICAL TRIALS). These indications are subject to review / potential modification prior to inclusion of trametinib dimethyl sulfoxide in the ARTG.
- Toxicity has been taken into account in consideration of benefit – risk.
- The aspects of dosage, formulation, labelling, packaging and presentation have been evaluated and found acceptable in the TGA evaluation process.
- The potential for abuse of this substance is limited.

Schedule entry

Schedule 4 – New Entry

TRAMETINIB DIMETHYL SULFOXIDE.

5.8 TRASTUZUMAB EMTANSINE

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the

Trastuzumab emtansine is an antibody-drug conjugate consisting of the antibody trastuzumab (a prescription-only medicine) linked to the cytotoxic agent DM1 that is a derivative of maytansine.

Trastuzumab emtansine is indicated, as a single agent, for the treatment of patients with HER2-positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: received prior therapy for metastatic disease; or developed disease recurrence during or within 6 months of completing adjuvant therapy.

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Trastuzumab emtansine is not specifically scheduled in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Trastuzumab emtansine is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegates' final decision

The delegate has made a final decision to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* to include trastuzumab emtansine in Schedule 4, with an implementation date of 1 Feb 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) risks and benefits; (b) purpose and the extent of use and (c) toxicity, d) dosage, formulation, labelling, packaging and presentation, and (e) the potential for abuse of trastuzumab emtansine.

The delegate decided that the reasons for the final decision comprise of the following.

- Trastuzumab emtansine is a new chemical entity with no marketing experience in Australia.
- During the TGA evaluation process, the benefits have been found to outweigh the risks of use in the indicated population.
- Trastuzumab emtansine is indicated, as a single agent, for the treatment of patients with HER2-positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: received prior therapy for metastatic

disease; or developed disease recurrence during or within 6 months of completing adjuvant therapy.

- Toxicity has been taken into account in consideration of benefit – risk.
- The aspects of dosage, formulation, labelling, packaging and presentation have been evaluated and found acceptable in the TGA evaluation process.
- The potential for abuse of this substance is limited.

Schedule entry

Schedule 4 – New Entry

TRASTUZUMAB EMTANSINE.

6. Editorials and errata

6.1 BISTRIFLURON

Scheduling Proposal

The chemicals scheduling delegate (the delegate) considered a proposal from the Scheduling Secretariat to amend the incorrect 'area of use' 1.1.2 in Part3 of the Appendix B for bistrifluron in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) to correct area of use 1.2.2 as listed in Part 1 of the Appendix B.

The delegate has considered this application and made a delegate-only decision. The Advisory Committee on Chemicals Scheduling was not consulted.

Scheduling Status

- Bistrifluron is currently included in Appendix B of the SUSMP.
  - The reason of entry is low toxicity 'a'.
  - The area of use is Agricultural '1.1.2'.

Delegate's Consideration

The delegate considered the following with regard to this proposal.

- Delegate-only final decision on Bistrifluron dated on 17 April 2012.
- The Amendment No 3.2 of the SUSMP.
- The Appendix B, Part 1 of the SUSMP.
  - The area of use for termiticide is '1.2.2'
- The Scheduling Policy Framework.

Delegate's Final Decision

The delegate has made a delegate-only decision to correct a typographical error in the entry for bistrifluron in the Part 3 of the Appendix B in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

The reason for the delegate's decision is to correct a typographical error.

The amendment will be included in the next amendment of the SUSMP, which implementation date is 1 February 2014.

Appendix	Title	Reason for listing	Area of use
Bistrifluron - Amend entry to read:			
B	Bistrifluron	a	1.2.2

6.2 BESIFLOXACINE HYDROCHLORIDE, LOTEPREDNOL ETABONATE, PASIREOTIDE DIASPARTATE AND VILANTEROL TRIFENATATE

Scheduling Proposal

The medicines scheduling delegate (the delegate) considered a proposal from the Scheduling Secretariat to amend besifloxacine hydrochloride, loteprednol etabonate, pasireotide diaspartate and vilanterol trifenatate to list the parent substance rather than the individual salt (and esters). By scheduling the parent substance, it avoids the necessity to reconsider the scheduling when another salt, ester, etc. appears.

The delegate has considered this application and made a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling Status

Besifloxacine hydrochloride, loteprednol etabonate, pasireotide diaspartate and vilanterol trifenatate are all listed in Schedule 4.

Delegate's Consideration

The delegate considered the following with regard to this proposal:

· The proposal;

· General scheduling policy.

Delegate's Final Decision

The delegate has made a delegate-only decision to list the parent substance for the following substances:

· besifloxacine hydrochloride;

· loteprednol etabonate;

· pasireotide diaspartate; and

· vilanterol trifenatate.

The reason for the delegate's decision is to:

· provide consistency in the scheduling of substances; and

· avoiding the necessity to reconsider the scheduling entry should another salt or ester appears.

The implementation date is 1 February 2014.

Schedule entry

Schedule 4 – Amendment

BESIFLOXACINE.

LOTEPREDNOL.

PASIREOTIDE.

VILANTEROL.