Australian Government
Department of Health
Therapeutic Goods Administration

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

16 January 2017

(Chemicals not referred to the November 2016 ACCS and New Chemical Entities)

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

The delegates of the Secretary to the Department of Health hereby give 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 the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (implementation date) of the decision.

The delegates' final decisions and reasons relate to scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the *Scheduling Policy Framework for Chemicals and Medicines* (SPF, 2015), available at SPF, February 2015.

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the *Poisons Standard* are published electronically on the Federal Register of Legislation (FRL) as amendments to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the *Poisons Standard* on the Federal Register of Legislation (FRL), is available at SUSMP.

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 (now Biosecurity)
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
CAS	Chemical Abstract Service

Abbreviation	Name
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)
EU	European Union
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 of Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network

Abbreviation	Name
IMAP	Inventory Multi-tiered Assessment Prioritisation
INN	International Non-proprietary Name
IUPAC	International Union of Pure and Applied Chemistry
ISO	International Standards Organization
LC_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50 per cent 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

Abbreviation	Name
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])
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

Abbreviation	Name
SPF	Scheduling Policy Framework
STANZHA	States and Territories and New Zealand Health Authorities
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working party
WS	Warning statement

Contents

Final decisions on matters not referred to an expert advisory committee

1. Chemicals not referred to the November 2016 ACCS

Summary of delegates' final decisions

Substance	Final Decision
m-Aminophenol	**Schedule 6 – New Entry** *m*-AMINOPHENOL **except** when in hair dye preparations containing 1.2 per cent or less of *m*-aminophenol when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. written in letters not less than 1.5 mm in height. **Appendix E, Part 2 –** *m*-AMINOPHENOL Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 –** *m*-AMINOPHENOL Warning statements: 28 ((over) (repeated) exposure may cause sensitisation). Implementation date: **1 February 2017**.
1,3-Benzenediol	**Schedule 6 – New Entry** RESORCINOL **except**: a) in hair dye preparations containing 1.25 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. written in letters not less than 1.5 mm in height; or

Substance	Final Decision
	b) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement: WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used on the eyelashes or eyebrows; to do so may be injurious to the eye. written in letters not less than 1.5 mm in height. **Appendix E, Part 2 –** RESORCINOL Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 –** RESORCINOL Warning statements: 28 ((over) (repeated) exposure may cause sensitisation). **Index – New Entry** RESORCINOL cross reference: 1,3-benzenediol Schedule 6 Appendix E, Part 2 Appendix F, Part 3 Implementation date: **1 February 2017**.
2-Chloro-6-(ethylamino)-4-nitrophenol	**Schedule 6 – New Entry** 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except** when in hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and written in letters not less than 1.5 mm in height. **Appendix E, Part 2 –** 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor

Substance	Final Decision
	(at once)], E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 –** 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL Warning statements: 28 ((over) (repeated) exposure may cause sensitisation). Implementation date: **1 February 2017**.
2,4-Diaminophenoxyethanol hydrochloride	**Schedule 6 – Amend Entry** 2,4-DIAMINOPHENOXYETHANOL (including its salts) **except:** a) in non-oxidative hair dye preparations containing 4 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and written in letters not less than 1.5 mm in height; or b) in oxidative hair dye preparations containing 2 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – Current Entry** 2,4-DIAMINOPHENOXYETHANOL Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 – Amend Entry** 2,4-DIAMINOPHENOXYETHANOL Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Substance	Final Decision
	Implementation date: **1 February 2017**.

1.1 *m*-Aminophenol

Referred scheduling proposal

An application was submitted to create a new Schedule 6 entry for *m*-aminophenol and to determine whether an appropriate exemption cut-off is required.

Current scheduling status and relevant scheduling history

m-Aminophenol is not currently scheduled and has not previously been considered for scheduling; therefore, a scheduling history is not available.

Isomers of *m*-aminophenol, *o*- and *p*-aminophenol have been considered for scheduling:

o-Aminophenol

In July 2014, the Advisory Committee on Chemicals Scheduling (ACCS) advised that *o*-aminophenol does not require scheduling.

p-Aminophenol

In March 2016, the ACCS advised that *p*-aminophenol be listed in Schedule 6 except when used in hair dye and eyebrow/eyelash colouring products. Effective 1 October 2016 the schedule for *p*-aminophenol will be as follows:

Schedule 6

p-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less of *p*-aminophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – *p*-AMINOPHENOL

Standard statements: A, S1.

Appendix F, Part 3 – *p*-AMINOPHENOL

Warning Statement: 28.

Homologues of *m*-aminophenol, 4-amino-*m*-cresol and 4-amino-2-hydroxytoluene, are listed with reference to use in hair dyes with a 1.5 per cent or less cut-off in the SUSMP as follows:

4-Amino-m-cresol

Schedule 6

4-AMINO-m-CRESOL in hair dyes and eyebrow/eyelash colouring preparations **except**:

a) in hair dye preparations containing 1.5 per cent or less of 4-amino-m-cresol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5mm in height; or

b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 4-amino-m-cresol after mixing for use when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – 4-AMINO-*m*-CRESOL

Standard statements: A, E1.

Appendix F, Part 3 – 4-AMINO-*m*-CRESOL

Warning statement: 28.

4-Amino-2-hydroxytoluene

Schedule 6

4-AMINO-2-HYDROXYTOLUENE in hair dyes and eyebrow/eyelash colouring products **except**:

a) in hair dye preparations containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5mm in height; or

b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – 4-AMINO-2-HYDROXYTOLUENE

Standard statements: A, E1.

Appendix F, Part 3 – 4-AMINO-2-HYDROXYTOLUENE

Warning statement: 28.

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5-AMINO-*o*-CRESOL
cross reference: 4-AMINO-2-HYDROXYTOLUENE

Australian regulatory information

New Zealand, ASEAN countries and the EU have restricted the use of *m*-aminophenol in cosmetics (see *International regulations* below); however, there are currently no restrictions in Australia on the use of the chemical in cosmetics or domestic products.

Considering the use of this chemical in permanent hair dyes in Australia and other potential domestic uses (based on overseas information), the main routes of public exposure are expected to be through the skin and inhalation from products applied as aerosols.

In the absence of regulatory controls, the characterised critical health effects (acute toxicity and skin sensitisation) have the potential to pose an unreasonable risk under the identified uses. The risk could be mitigated by implementing restrictions for the use of the chemical in hair dyes and other cosmetic products.

International regulations

Use of the chemical in cosmetics in the EU is subject to the restrictions described in EU Cosmetics Regulation 344/2013 (as an amendment to the listing under Annex III of Regulation 1223/2009). The use of the chemical in hair dyes is restricted to a maximum concentration of 1.2% applied to hair after mixing under oxidative conditions (1:1 ratio with hydrogen peroxide). If the chemical is present at lower concentrations, sensitisation labelling is required.

Use of the chemical in cosmetics and domestic products is also restricted in several other countries as follows:

- ASEAN Cosmetic Directive Annex III Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions; and
- New Zealand Cosmetic Products Group Standard—Schedule 5, Table 1: Components cosmetic products must not contain except subject to restrictions and conditions.

Under the above regulations, the use of the chemical in hair dyes is restricted to a maximum concentration of 1.2% applied to hair after mixing under oxidative conditions.

Scheduling application

General application.

The application's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

m-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1.2 per cent or less of *m*-aminophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – *m*-AMINOPHENOL

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – *m*-AMINOPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- Currently, there are no restrictions on introducing or using this chemical in Australia. In the absence of any regulatory controls, the characterised critical health effects (particularly skin sensitisation) have the potential to pose an unreasonable risk if *m*-aminophenol is used in cosmetic products without an appropriate concentration cut-off (exemption) for hair dye use. Whilst domestic use of the chemicals will result in lower levels of exposure, there is sufficient uncertainty regarding the safety of such products to warrant some restriction;
- *m*-Aminophenol was reported to be used in permanent hair dye preparations in Australia, and overseas hair products and other personal care products;
- *m*-Aminophenol is a contact allergen in humans;
- *m*-Aminophenol is a strong skin sensitiser in animals, based on a local lymph node assay (LLNA)-derived EC3 (estimated concentration to produce a three-fold increase in lymphocyte proliferation) value of 0.24-3.2%;
- The existing overseas restrictions (Association of Southeast Asian Nations (ASEAN), New Zealand, European Union (EU)) on the use of the chemical in cosmetic products, where the use of *m*-aminophenol in hair dyes is restricted to a maximum concentration of 1.2% applied to hair after mixing under oxidative conditions (a 1:1 mixture of 2.4% 3-aminophenol with hydrogen peroxide); and
- When *m*-aminophenol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Substance summary

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment report for 3-aminophenol. Further information can also be found in the SCCP report for m-aminophenol.

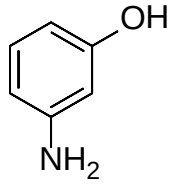


Figure 1.1: Chemical structure of *m*-aminophenol

Table 1.1A: Chemical properties and identifiers of *m*-aminophenol

Property/identifier	*m*-Aminophenol
Molecular formula	C_6H_4
Molecular weight	109.13 g/mol
CAS name	Phenol, 3-amino-
CAS number	591-27-5
IUPAC and/or common and/or other names	3-hydroxyaniline (IUPAC); *m*-aminophenol (INCI)
SUSMP name	Not listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Based on previously considered isomers, *p*-aminophenol (March 2016 ACCS meeting cycle) and o-aminophenol (July 2014 ACCS meeting cycle), the recommended SUSMP name is *m*-aminophenol.

Table 1.1B: Acute toxicity end-points for *m*-aminophenol

Toxicity	Species	*m*-Aminophenol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bodyweight (bw))	Rat	812-1000	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	1162	Schedule 6
Skin irritation	Rabbit	No irritation (2% *m*-aminophenol in a suspension of 0.5% methylcellulose in purified water)	N/A
Eye irritation	Rabbit	Mild irritation (2% *m*-aminophenol in a suspension of 0.5% methylcellulose in purified water)	N/A

Toxicity	Species	*m*-Aminophenol	SPF (2015) Classification
Skin sensitisation (LLNA)	Mouse	Moderate to strong skin sensitiser (EC3 0.24-3.2%)	Schedule 6
Skin sensitisation (Guinea pig maximisation test (GPMT))	Guinea pig	Sensitiser. Positive reactions in 100% of animals tested at 5%, following 1% intradermal induction and 1% topical induction.	

Acute toxicity

m-Aminophenol has moderate acute oral and inhalation toxicity, warranting hazard classification. No data were available for acute dermal toxicity.

Irritation

The available data from animal and human studies indicate that the chemical is not irritating to the skin or eyes.

Sensitisation

Based on the available animal and human data, the chemical is considered to be a moderate to strong skin sensitiser and is recommended for classification.

- In an in vivo mouse LLNA conducted in accordance with OECD Test Guideline (TG) 429, 28 female CBA/J mice (four animals/group) were administered the chemical at concentrations of 0, 1, 2.5, 5, 10 or 25% (w/v) in dimethylformamide. Stimulation indices (SI) of 0, 7.6, 12.6, 10.4, 7.2 and 6.0 were reported, respectively. In a second experiment, concentrations of 0, 0.05, 0.1, 0.5, 1.0 and 2.5% of the chemical in the same vehicle were administered to the animals. SIs of 1.0, 1.4, 5.9, 9.0 and 11.0 were reported, respectively. The calculated EC3 value (0.24%) indicated strong sensitisation potential for the chemical.

- In another mouse LLNA study, CBA/Ca mice were administered the chemical at concentrations of 0, 2.5, 5 or 10% (w/v) in acetone/olive oil (ratio of 4:1). SIs of 0, 2.8, 3.5 and 5.7 were reported, respectively. The EC3 value was reported to be 3.2%.

- In a non-guideline GPMT, guinea pigs were administered the chemical at a concentration of 1.0% (v/v) in acetone/olive oil (ratio of 4:1) by intradermal injection, followed by topical induction with a 10% solution of the chemical one week later. After two weeks, a topical challenge dose of 5% resulted in positive reactions observed in all animals tested.

Repeat-dose toxicity

Based on the available information, *m*-aminophenol is not considered to cause serious damage to health through repeated oral exposure at low doses. Systemic toxicity has not been demonstrated via the dermal route. No information was available for repeated dose toxicity by inhalation.

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, *m*-aminophenol is not considered to be genotoxic.

Carcinogenicity

Based on the available data and the lack of genotoxicity, *m*-aminophenol is not expected to be carcinogenic.

Reproduction and developmental toxicity

Based on the available information, *m*-aminophenol is not expected to be a reproductive or developmental toxin.

Observation in humans

Sensitisation:

Sensitisation in humans exposed to the chemical has been observed both in repeat insult patch tests and during diagnostic patch testing.

In two semi-occlusive repeat insult patch tests, 0.1 mL doses of *m*-aminophenol (3% solution in Schultz vehicle II or similar) were applied to the backs of 98 and 99 test subjects over a six week period. There were 10 consecutive induction patch applications at 48–72 hours, followed by one day of no application. Challenge patch applications on previously unexposed skin on backs of humans were conducted 48 hours following the rest period. In both studies, irritant effects (erythema) were observed in several subjects during the induction phase. In the first study (98 subjects), no reactions to the challenge patches were observed. In the second study (99 subjects), two subjects showed reactions following application of the challenge patches, as well as following application of additional rechallenge patches on different parts of the body.

In an Australian case study, 164 hairdressers and hairdressing apprentices who presented with allergic contact dermatitis at a dermatology clinic were patch-tested against 36 chemicals used in hair salons. Four subjects, previously exposed to *m*-aminophenol in the workplace, had positive reactions when patch tested with the chemical.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- scheduling proposal
- NICNAS IMAP Tier II Report
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015) criteria
- other relevant information.

Delegate's final decision

The final decision is to create a new Schedule 6 entry for *m*-aminophenol with a 1.2 per cent exemption cut-off in hair dye preparations as follows:

Schedule 6 – New Entry

m-AMINOPHENOL **except** when in hair dye preparations containing 1.2 per cent or less of *m*-aminophenol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – *m*-AMINOPHENOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – *m*-AMINOPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The delegate notes that oxidative hair dyes of the aminophenolic class have common toxicological properties that warrant controls over scheduling. Exposure to *m*-aminophenol exposure may occur dermally or through inhalation from aerosol products. The acute oral and inhalational toxicity and skin sensitisation of *m*-aminophenol are consistent with SFP criteria for Schedule 6. Recent decisions for previously considered similar sensitising hair dyes have allowed for some products to be exempted where there are label statements warning of the potential for skin sensitisation, and recommending testing for individual susceptibility before use. This scheduling decision is in alignment with international regulations for *m*-aminophenol and is consistent with recent decisions agreed on previously considered similar sensitising hair dyes.

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

The implementation date is **1 February 2017**.

1.2. 1,3-Benzenediol

Referred scheduling proposal

An application was submitted to create a new Schedule 6 entry for 1,3-benzenediol for restriction in cosmetic and domestic products.

Current scheduling status and relevant scheduling history

1,3-Benzenediol is not currently scheduled and has not been previously considered for scheduling; therefore, a scheduling history is not available. However, an isomer of 1,3-benzenediol, 1,2-benzenediol is currently scheduled as follows:

Schedule 6

1,2-BENZENEDIOL.

Appendix E – 1,2-BENZENEDIOL (catechol)

Standard statements: A, E1, S1

Appendix F – 1,2-BENZENEDIOL (catechol)

Warning statements: 51, 59.

Safety directions: 1, 4, 8.

Australian regulatory information

1,3-Benzenediol was reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007) and in overseas hair lotions and shampoos.

Currently, there are no restrictions in Australia on using this chemical in hair dyes, hair lotions and shampoos. In the absence of any regulatory controls, the characterised critical health effects (skin and

eye irritation, and skin sensitisation) have the potential to pose an unreasonable risk under the identified uses. The risk could be mitigated by implementing concentration limits and labelling requirements for use in hair dyes, hair lotions and shampoos.

International regulations

The EU has restricted the use of this chemical in oxidative hair colouring products at a maximum concentration of 2.5%. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, which corresponds to a concentration of 1.25% when applied to hair (SCCS, 2010). Restricted use in hair lotions and shampoos was also reported to be the maximum authorised concentration in the finished cosmetic product of 0.5%.

1,3-Benzenediol is listed on the EU Cosmetic Directive 76/768/EEC Annex III Part 1: List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down below (Galleria Chemica): (a) Hair dye substance in oxidative hair dye products for general and professional use—after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.25% (w/w); and (b) Hair lotions and shampoos— maximum authorised concentration in the finished cosmetic product of 0.5% (w/w).

1,3-Benzenediol is also listed on the following:

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist'); and
- Chile list of Cosmetic Ingredients with limited use or concentration.

Scheduling application

General application.

The application's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

1,3-BENZENEDIOL **except**:

a) in hair dye preparations containing 1.25 per cent or less of 1,3-benzenediol after mixing for use and when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height; or

b) in hair lotions/shampoo products containing 0.5 per cent or less of 1,3-benzenediol and when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E – 1,3-BENZENEDIOL

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F – 1,3-BENZENEDIOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- 1,3-Benzenediol is used in permanent hair dye preparations in Australia (NICNAS, 2007) and in hair lotions and shampoos overseas (refer to Import, Manufacture and Use section of IMAP Tier II report);
- 1,3-Benzenediol has moderate oral toxicity and has been shown to cause skin and eye irritation as well as skin sensitisation;
- 1,3-Benzenediol has existing overseas restrictions in European Union (EU) for oxidative hair colouring products at a maximum concentration of 2.5%, with labelling requirements at lower concentrations. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, resulting in a concentration of 1.25% when applied to hair (SCCS, 2010). Use of the chemical is also restricted in hair lotions and shampoos with a maximum authorised concentration in the finished cosmetic product of 0.5%; and
- When 1,3-benzenediol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Substance summary

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment. Further information can also be found in the European Commission Scientific Committee on Consumer Safety (SCCS) report.

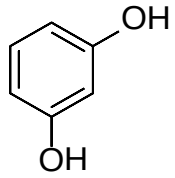


Figure 1.2: Chemical structure of 1,3-benzenediol

Table 1.2A: Chemical properties and identifiers of 1,3-benzenediol

Property/identifier	1,3-Benzenediol
Molecular formula	$C_6H_6O_2$
Molecular weight	110.1 g/mol
CAS name	1,3-Benzenediol

Property/identifier	1,3-Benzenediol
CAS number	108-46-3
IUPAC and/or common and/or other names	Resorcinol (INCI name); benzene-1,3-diol (IUPAC); 1,3-dihydroxybenzene; and 3-hydroxyphenol.

Table 1.2B: Acute toxicity end-points for 1,3-benzenediol

Toxicity	Species	1,3-Benzenediol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats (Sprague Dawley)	200-980 mg/kg bw/day.	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits	> 2000 mg/kg bw/day.	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rats (Harlan Wistar)	> 7800 mg/m 3/1–hour (equivalent to 7.8 mg/L or 1732 ppm); and > 2800 mg/m 3/8–hours (equivalent to 2.8 mg/L or 622 ppm)	N/A
Skin irritation	Rabbit (albino)	Slight to severe skin irritant in diluted and semi-solid state, respectively (flaked and industrial grade).	Schedule 6
	Rabbit (New Zealand White)	Not irritating to skin (2.5% solution in water; 98.8% purity)	
Eye irritation	Rabbit (albino)	Severe eye irritant (see below)	Schedule 6
Skin sensitisation (Guinea Pig Maximisation Test: GPMT)	Guinea pigs (Pirbright white)	Sensitiser (relative incidence of the positive reactions in animals was > 30%) (99.9% purity)	Schedule 6

Toxicity	Species	1,3-Benzenediol	SPF (2015) Classification
Skin sensitisation (mouse local lymph node assay: LLNA)	Mice (CBA/Ca)	Moderate sensitiser with EC = 1.4 and 6.3% (unspecified purity)	

Acute toxicity

The acute toxicity end-points of 1,3-benzenediol are summarised in Table 1.2B.

Skin irritation

Based on the weight of evidence, the chemical is considered to be slightly to severely irritating to skin when administered diluted in an aqueous solution or in semi-solid state (flaked or industrial grade):

- In a non-guideline (Federal Hazardous Substance Labelling Act (FHSLA)) skin irritation study, 0.5 g of the chemical (flaked grade) in saline was applied to the clipped belly skin (abraded and intact) of albino rabbits (six males) for 24 hours under occlusive patches. Observations were made at 24 and 72 hours post-treatment, and animals were kept under observation for a maximum of two weeks. Treatment-related effects were moderate irritation on intact skin and necrosis on abraded skin. Effects were more pronounced at 72 hours post-treatment. In the two week recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) was reported to be 4.4;

- In similar non-guideline (FHSLA) studies, a 24-hour occluded application of the chemical (flaked and industrial grade) at 0.5 g to the bellies of male albino rabbits produced moderate irritation on intact skin and necrosis on abraded sites. The chemical (industrial grade) was reported to cause slight to severe irritation of the intact areas, and from severe irritation to necrosis of the abraded areas, 24 hours after exposure. In the 2-week post-recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) for the chemical was reported to be 4.4 (flaked grade) and 5.4 (industrial grade); and

- In a study conducted according to the OECD Test Guideline 404 (acute dermal irritation/corrosion), 0.5 mL of the chemical (2.5% aqueous solution) (98.8% purity) was applied to the clipped back skin of New Zealand White rabbits (three males/group) for four hours under semi-occlusive patches. Observations were made at one, 24, 48 and 72 hours post-treatment. No adverse cutaneous reactions were reported at this low concentration.

Eye irritation

Data from one study using the chemical (flaked and industrial grade diluted in an aqueous solution and semi-solid state, respectively) indicated that the chemical should be considered a severe eye irritant:

- In a non-guideline (FHSLA) study, 0.1 g of the chemical (flaked and industrial grade) was instilled into the eyes of albino rabbits (6 males). Treatment-related effects upon administration included inflamed conjunctivae, opaque corneas and visible discomfort in animals. At 24 hours post-exposure, observations included severe conjunctivitis, iritis, corneal opacity occluding most of the iris and corneal ulcerations. Irreversible effects on the eyes were reported and by day 14, all treated eyes had kerataconus (thinning of and irregularly shaped cornea) and pannus (abnormal layer of fibrovascular tissue or granulation tissue over the cornea) formation. Total mean eye irritation Draize scores were reported to be 105/110 at 24, 48 and 72 hours and the chemical was considered to be a severe eye irritant;

- The chemical was mildly irritating in six albino rats administered 0.1 g of the chemical (dry powder). Reported mean irritation scores were 56.3, 45.0 and 39.9 out of 110 over the observation period at 24, 48 and 72 hours, respectively. No further study details were available; and

- In a study conducted according to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of the chemical (2.5% solution in water (98.8% purity)) was instilled into the eyes (conjunctival sacs) of New Zealand White rabbits (three males) and left for 72 hours. Mean scores of zero were reported for chemosis, iris lesions and corneal opacity over 24, 48 and 72 hours. For redness of the conjunctivae, a mean score of 0.1 was reported.

Skin sensitisation

Based on the available animal and human data, the chemical is considered to be a moderate to strong contact skin sensitiser and is recommended for classification:

- In a GPMT conducted in accordance with OECD TG 406, Pirbright white guinea pigs (treatment group 10 animals, control group 5 animals and accompanying group 20 animals used for range finding) were administered 2% (w/v) solution of the chemical (99.9% purity as white flakes in sodium chloride) by intradermal injection followed by occlusive, epicutaneous application of 25% the chemical. At the challenge exposure using 25% of the chemical (occlusive epicutaneous application), very slight to distinct erythema was observed on the skin of 2-3 animals at 24 and 48 hours observation periods. At the second challenge and compared to the control group, very slight to distinct erythema was reported in 7/10 guinea pigs at 24 hours and on 5/10 guinea pigs at 48 hours and minor swelling was also observed in one animal at 24 hours after patch removal. The relative incidence of the positive reactions in animals was over the threshold value of 30% and the chemical was considered to be a skin sensitiser;

- In a study conducted in accordance with OECD TG 429, positive skin sensitisation was reported in LLNA studies in two independent experiments. A positive control of a-hexyl cinnamaldehyde (HCA), a moderate sensitiser, at the concentration of 25% (v/v) in DMF was used. In the first experiment (range finding), female CBA/J mice (four animals/dose including negative and positive controls) were administered 25 µL of the chemical (in vehicle dimethylformamide at 2.5, 5, 10, 25 or 50%) applied to the dorsal surface of each ear, once daily for three consecutive days. Stimulation indices (SI) of 3.83, 4.14, 3.97, 3.51 and 3.30 were reported, respectively. Positive lymphoproliferative responses (SI > 3) were reported at all concentrations, but no clear dose-response relationship was observed. In the second experiment, mice (four/dose) were administered daily applications of 0.1, 0.5, 1, 5 or 25% chemical (w/v). Treatment resulted in stimulation indices of 1.58, 2.87, 1.97, 3.51 and 5.74, respectively. A dose-related increase in SI was seen and the threshold positive value of three was exceeded. The effective concentration at which a three-fold increase in SI was achieved (EC3) was reported to be 1.4% and the chemical was considered to be a moderate skin sensitiser; and

- The chemical (purity unspecified) was not reported to be sensitising according to two non-guideline skin sensitisation (LLNA) studies in mice (concentrations of up to 2.5% and 25% w/v were tested, respectively). No further study details were available and the reliability of both studies was questioned due to out-dated study methods (OECD, 2008). However, the chemical was reported to be a sensitiser in mice in a LLNA study (OECD TG 429). A group of CBA/Ca female mice (four/dose) were treated at daily concentrations of 0, 1, 5, 10, 25 and 50% (w/v) of the chemical (purity unspecified) in acetone/olive oil (ratio of 4:1). SIs of 1.0, 0.7, 2.2, 5.2, 8.4 or 10.4 were measured respectively, and an EC value of 6.3% was determined (REACH; OECD, 2008).

Observation in humans

Human patch-testing using 1,3-benzenediol elicited allergic skin reactions in 0.7–0.8% of 1694 dermatitis patients. In further case histories of 34 dermatitis patients, the chemical was reported to cause reactions after epicutaneous testing.

No dermatitis of the hands was reported for 42 workers from a tyre factory after an epicutaneous test with the chemical.

In human patch tests with the chemical (2% in petrolatum), four out of 302 hairdressers suffering from contact dermatitis reported a positive reaction. No further details were available. In another case, one patient who developed contact dermatitis after application of paint to the skin was patch tested with the chemical (5% in petrolatum) and showed a positive result after 48 hours. In a third case, three female patients suffering from acne and contact dermatitis gave a positive patch test for the chemical (2% in petrolatum) after 48 and 72 hours.

Repeat-dose toxicity

Based on the weight-of-evidence, the chemical is not considered to cause serious damage to health from repeated oral exposure.

No information was available for repeated dose toxicity by the dermal route.

There is insufficient evidence to evaluate repeated dose inhalation toxicity.

Genotoxicity

Based on the weight-of-evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, the chemical is not considered to be a reproductive or developmental toxin.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- NICNAS IMAP Tier II Report;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015) criteria; and
- Other relevant information.

Delegate's final decision

The delegate's final decision is to create a new Schedule 6 entry for 1,3-benzenediol with a 1.25 per cent exemption cut-off in hair dye preparations as follows:

Schedule 6 – New Entry

RESORCINOL **except**:

a) in hair dye preparations containing 1.25 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the

accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

b) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used on the eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – RESORCINOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – RESORCINOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index – New Entry

RESORCINOL
cross reference: 1,3-benzenediol

Schedule 6
Appendix E, Part 2
Appendix F, Part 3

The delegate notes that the main routes of exposure to resorcinol is through the skin and eyes from products applied to the hair and scalp. The skin and eye irritation and skin sensitisation of resorcinol are consistent with Schedule 6 criteria. Recent decisions for previously considered similar sensitising hair dyes have allowed for some products to be exempted where there are label statements warning of the potential for skin irritancy and sensitisation, and recommending testing for individual susceptibility before use. This scheduling decision is in alignment with international regulations for resorcinol and is consistent with recent decisions agreed on previously considered similar sensitising hair dyes.

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

The implementation date is **1 February 2017**.

1.3. 2-Chloro-6-(ethylamino)-4-nitrophenol

Referred scheduling proposal

An application was submitted to create a new entry for 2-chloro-6-(ethylamino)-4-nitrophenol in Schedule 6 to restrict its use in hair dyes and to determine whether an appropriate exemption concentration cut-off is required.

Current scheduling status and relevant scheduling history

2-Chloro-6-(ethylamino)-4-nitrophenol is not currently scheduled and has not been previously considered for scheduling; therefore, scheduling history is not available.

However, a homologue of 2-chloro-6-(ethylamino)-4-nitrophenol, 2-amino-6-chloro-4-nitrophenol is currently listed in Schedule 6 for use in hair dye and eyebrow/eyelash colouring preparations as follows:

Schedule 6

2-AMINO-6-CHLORO-4-NITROPHENOL in hair dye and eyebrow/eyelash colouring preparations, **except**:

a) in preparations containing 2 per cent or less of 2-amino-6-chloro-4-nitrophenol when applied directly to the hair, or containing 2 per cent or less of 2-amino-6-chloro-4-nitrophenol after mixing and when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN; and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 2-amino-6-chloro-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – 2-AMINO-6-CHLORO-4-NITROPHENOL

Standard statements: A, E1.

Appendix F, Part 3 – 2-AMINO-6-CHLORO-4-NITROPHENOL

Warning statement: 28.

International regulations

Use of the chemical in cosmetics in the European Union (EU) is subject to the restrictions described in EU Cosmetics Regulation 344/2013 (as an amendment to the listing under Annex III of Regulation 1223/2009). This chemical may be used at maximum concentrations of 3.0% in ready-for-use preparations of oxidising (permanent) and non-oxidising (semi-permanent) colouring agents for hair dyeing. Additionally, after mixing under oxidative conditions (i.e. with hydrogen peroxide) the maximum concentration applied to hair must not exceed 1.5% for both permanent and semi-permanent application types. The Cosmetics Regulation also mandates label warning statements relating to the sensitisation potential of the chemical.

Use of the chemical in hair dyes is also restricted in several other countries as according to inclusion in the following listings:

- the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1, with the same use restrictions as described above for the EU; and
- the New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to restrictions and conditions laid down. While a maximum concentration (of 3.0%) only appears to apply to ready for use preparations of non-

oxidising (semi-permanent) colouring agents for hair dyeing, the maximum concentration applied to hair must not exceed 1.5% for both permanent and semi-permanent application types.

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

Schedule 6 – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use and when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- Reported use of 2-chloro-6-(ethylamino)-4-nitrophenol as an ingredient in both permanent and semi-permanent hair dyes in Australia;
- 2-Chloro-6-(ethylamino)-4-nitrophenol is a skin sensitiser;
- 2-Chloro-6-(ethylamino)-4-nitrophenol is acutely toxic following oral exposure;
- Overseas restrictions for use of 2-chloro-6-(ethylamino)-4-nitrophenol in hair dyes; and
- When 2-chloro-6-(ethylamino)-4-nitrophenol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Substance summary

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment report for phenol, 2-chloro-6-(ethylamino)-4-nitro-.

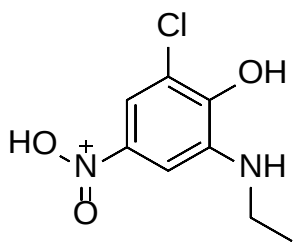


Figure 1.3: Chemical structure of 2-chloro-6-(ethylamino)-4-nitrophenol

Table 1.3A: Chemical properties and identifiers of 2-chloro-6-(ethylamino)-4-nitrophenol

Property/identifier	2-Chloro-6-(ethylamino)-4-nitrophenol
Molecular formula	$C_8H_9ClN_2O_3$
Molecular weight	216.62 g/mol
CAS name	Phenol, 2-chloro-6-(ethylamino)-4-nitro-
CAS number	131657-78-8
IUPAC and/or common and/or other names	2-Chloro-6-(ethylamino)-4-nitrophenol (INCI name)

Table 1.3B: Acute toxicity end-points for 2-chloro-6-(ethylamino)-4-nitrophenol

Toxicity	Species	2-Chloro-6-(ethylamino)-4-nitrophenol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1728	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	Schedule 5
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	-	No data	N/A
Skin irritation	Rabbit	Not irritating to the skin	N/A
Eye irritation	Rabbit	Insufficient data.	N/A
Skin sensitisation (LLNA)	Mouse	Skin sensitiser	Schedule 6

Acute Toxicity

2-Chloro-6-(ethylamino)-4-nitrophenol has moderate acute oral toxicity, but low acute dermal toxicity based on results from animal tests. Additionally, the chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS. The available data support this classification.

Irritation

The available data from animal studies indicate that 2-chloro-6-(ethylamino)-4-nitrophenol is not irritating to the skin, but is a potential eye irritant. However, insufficient details on the eye irritation study are available, which do not allow for hazard classification.

Sensitisation

2-Chloro-6-(ethylamino)-4-nitrophenol is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in the HSIS. The positive results, reported in a local lymph node assay (LLNA), support this classification.

In an LLNA conducted according to OECD TG 429, the skin sensitising potential of 2-chloro-6-(ethylamino)-4-nitrophenol was tested in mice (5 animals/dose group) at concentrations ranging from 0.5–10% using a DMSO vehicle, and at 0.5–2.5% using an acetone/water/olive oil vehicle (mix ratio of 2:2:1). The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value of 2.79% was determined based on the concentrations used with the DMSO vehicle; a stimulation index greater than three was not observed at the lower concentrations used with the acetone/water/olive oil vehicle (up to 2.5%).

Repeat-dose toxicity

Based on the available information, 2-chloro-6-(ethylamino)-4-nitrophenol is not considered to cause serious damage to health through repeated oral exposure.

Mutagenicity/Genotoxicity

Based on the weight of evidence from the available, well-conducted, in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemical. Based on the available genotoxicity data and mechanistic information, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available information, the chemical is not expected to be a developmental toxin. No reliable data examining the effect of the chemical on fertility are available.

Observation in humans

No information was available.

Public exposure

Considering that the chemical is reported to be used in hair dye products in Australia, the main route of public exposure is expected to be dermal.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- NICNAS IMAP Tier II Report;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015) criteria; and
- Other relevant information.

Delegate's final decision

The delegate's final decision is to create a new Schedule 6 entry for 2-chloro-6-(ethylamino)-4-nitrophenol with a 1.5 per cent cut-off of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use in hair dye preparations as follows:

Schedule 6 – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except** when in hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The delegate notes that the main route of exposure to 2-chloro-6-(ethylamino)-4-nitrophenol is through the skin. The acute oral toxicity and skin sensitisation are consistent with Schedule 6 criteria. Recent decisions for previously considered similar sensitising hair dyes have allowed for some products to be exempted where there are label statements warning of the potential for skin sensitisation, and recommending testing for individual susceptibility before use. This scheduling decision is in alignment with international regulations for 2-chloro-6-(ethylamino)-4-nitrophenol and is consistent with recent decisions agreed on previously considered similar sensitising hair dyes.

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

The implementation date is **1 February 2017.**

1.4. 2,4-Diaminophenoxyethanol hydrochloride

Referred scheduling proposal

An application was submitted to create a new entry for 2,4-diaminophenoxyethanol hydrochloride in Schedule 6 with appropriate concentration cut-off for use in hair dyes.

Current scheduling status and relevant scheduling history

2,4-Diaminophenoxyethanol is already in Schedule 6 of the Poisons Standard as follows:

Schedule 6

2,4-DIAMINO-PHENOXYETHANOL in hair dye preparations except in preparations containing 4 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following:

KEEP OUT OF REACH OF CHILDREN

WARNING – this product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dying eyelashes and eyebrow; to do so may be injurious to the eye.

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – 2,4-DIAMINO-PHENOXYETHANOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (If in eyes wash out immediately with water.).

Appendix F, Part 3 - 2,4-DIAMINO-PHENOXYETHANOL

Warning statement: 21 (WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.).

Relevant scheduling history

In March 2014, the Advisory Committee on Chemicals Scheduling (ACCS) included 2,4-diaminophenoxyethanol in Schedule 6 and Appendices E and F of the Poisons Standard. Although the applicant's scheduling proposal specifically referenced the sulfate salt, it was noted at the meeting that the hydrochloride salt (2,4-diaminophenoxyethanol dihydrochloride) was used in the toxicity assessment and that the sulfate salt and free alcohol will likely have comparable physical/chemical and toxicological properties. The implementation date was 1 October 2014.

Australian regulatory information

2,4-Diaminophenoxyethanol hydrochloride is listed on the Australian Inventory of Chemical Substances (AICS) and is reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007).

International regulations

The Association of South East Asian Nations (ASEAN), Canada, New Zealand and the European Union (EU) have restricted the use of this chemical in cosmetics. Following a safety evaluation, the Scientific Committee on Consumer Products (SCCP) concluded that the use of the chemical 'as an oxidative hair dye at a maximum concentration of 2.0% in the finished cosmetic product (after mixing with hydrogen peroxide) does not pose a risk to the health of the consumer, apart from its sensitising potential' (SCCP, 2006).

The chemical is listed on the following:

- The ASEAN Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down: 'After mixing under oxidative conditions the maximum concentration applied to hair must not exceed 2.0% (as hydrochloride)';
- The EU Regulation (EC) No 1197/2013 of the European Parliament and of the Council of 1 July 2014 on cosmetic products Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: 'After mixing under oxidative conditions the maximum concentration applied to hair or eyelashes must not exceed 2.0% (as hydrochloride) and for professional use only'. The Cosmetic Regulation also mandates label warning statements relating to the sensitisation potential of the chemical;
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: 'In combination with hydrogen peroxide the maximum use concentration upon application is 2.0% as hydrochloride'; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

Schedule 6 – New Entry

2,4-DIAMINOPHENOXYETHANOL HYDROCHLORIDE **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 2 per cent or less of 2-(2,4-diaminophenoxy)ethanol hydrochloride after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – 2,4-DIAMINOPHENOXYETHANOL HYDROCHLORIDE

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – 2,4-DIAMINOPHENOXYETHANOL HYDROCHLORIDE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- 2,4-Diaminophenoxy)ethanol hydrochloride has overseas restrictions, where the maximum concentration allowed in hair and eyelash products must not exceed 2.0% (as hydrochloride) and for professional use only;
- 2,4-Diaminophenoxyethanol hydrochloride has reported cosmetic use in permanent hair dye preparations in Australia;
- 2,4-diaminophenoxyethanol hydrochloride has moderate oral acute toxicity, is an eye irritant and a moderate skin sensitiser;
- The risk could be controlled by including warning statements on the label of hair dye formulations containing 2,4-diaminophenoxyethanol hydrochloride at any concentration; and
- When 2,4-diaminophenoxyethanol hydrochloride is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Substance summary

The following information was extracted from the NICNAS IMAP Human Health Tier II group assessment report for Ethanol, 2-(2,4-diaminophenoxy)-, hydrochloride.

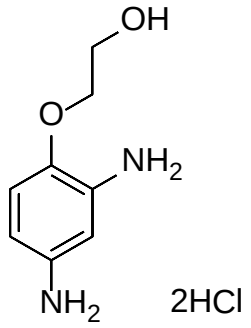


Figure 1.4: Structure of 2-(2,4-diaminophenoxy)ethanol hydrochloride

Table 1.4A: Chemical properties and identifiers of 2,4-diaminophenoxyethanol hydrochloride

Property/identifier	2,4-Diaminophenoxyethanol hydrochloride
Molecular formula	$C_8H_{12}N_2O_2.2HCl$
Molecular weight	241.119 g/mol
CAS name	ethanol, 2-(2,4-diaminophenoxy)-, hydrochloride (1:2)
CAS number	66422-95-5
IUPAC and/or common and/or other names	2,4-diaminophenoxyethanol HCL (INCI); 2,4-diaminophenoxyethanol hydrochloride.

Table 1.4B: Acute toxicity end-points for 2-(2,4-diaminophenoxy)ethanol hydrochloride

Toxicity	Species	2,4-diaminophenoxyethanol hydrochloride	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat Mouse	1000 1160	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	Rabbit	Non-irritant	N/A
Eye irritation	Rabbit	Irritant	Schedule 5/6
Skin sensitisation (local lymph node assay, LLNA)	Guinea pig Mouse	Moderate sensitiser	Schedule 6

Acute toxicity

The chemical is considered to have moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) was approximately 1000 mg/kg bw in Sprague Dawley (SD) rats and 1160 mg/kg bw in Swiss albino mice. No data were available for acute dermal and inhalation toxicity.

Skin Irritation

Based on the limited available data, the chemical is not considered to be a skin irritant.

Eye Irritation

Based on the available data, the chemical is considered to be an eye irritant:

- In an eye irritation study conducted according to OECD TG 405 with three female New Zealand White rabbits, the undiluted 2,4-diaminophenoxyethanol hydrochloride was instilled into the conjunctival sac of the left eye of each animal. The eyes were not rinsed following instillation of the chemical. Moderate to marked chemosis, slight to moderate conjunctival redness, slight to moderate corneal opacification and slight iridial lesions were observed in the animals. These effects were not fully reversed at the end of the study (day 15). It was concluded that the undiluted chemical was irritating to rabbit eyes.
- In two other eye irritation studies carried out in three female New Zealand White rabbits and three albino Bouscat rabbits, a 4% solution of the chemical did not produce any irritation.

Sensitisation

Based on the available data, the chemical is considered to be a moderate skin sensitiser:

- One LLNA was conducted according to OECD TG 429 in female CBA/J mice (n=4/group). The chemical at 0.5, 1.0, 2.5, 5.0 or 10% dilutions produced a stimulation index (SI) of 0.92, 1.56, 1.17, 4.21 and 7.42, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 3.2%, indicating a moderate sensitising potential.
- In a Buehler test (OECD TG 406) conducted using ten Dunkin Hartley guinea pigs per sex, no sensitisation reaction was observed with topical induction and challenge applications of the undiluted chemical after 48 hours.

Repeat-dose toxicity

Based on the available data, 2,4-diaminophenoxyethanol hydrochloride is not expected to cause serious damage to health from repeated oral exposure. No information was available for repeated dose toxicity by dermal and inhalation routes.

Genotoxicity

Based on the negative results observed in several in vitro and in vivo genotoxicity studies, the chemicals are not expected to be genotoxic.

Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, the chemical is not expected to have reproductive and developmental toxicity.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- NICNAS IMAP Tier II Report;
- Section 52E of the *Therapeutic Goods Act 1989*; and
- Scheduling Policy Framework (SPF 2015) criteria.

Delegate's final decision

The delegate's final decision is to amend the Schedule 6 entry for 2,4-diaminophenoxyethanol to include a 2 per cent exemption cut-off in oxidative hair dye preparations as follows:

Schedule 6 – Amend Entry

2,4-DIAMINOPHENOXYETHANOL (including its salts) **except:**

a) in non-oxidative hair dye preparations containing 4 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 2 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – Current Entry

2,4-DIAMINOPHENOXYETHANOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – Amend Entry

2,4-DIAMINOPHENOXYETHANOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The delegate notes that the main route of exposure to 2,4-diaminophenoxyethanol is through the skin, with acute oral toxicity, eye irritancy and skin sensitisation consistent with Schedule 6 SPF criteria. The amendment to include a concentration cut-off for use in oxidative hair dye preparations is consistent with international regulations (EU Regulation (EC) No 1197/2013 of 1 July 2014) and with recent newly scheduled and similarly sensitising hair dyes.

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

The implementation date is **1 February 2017**.

2. New Chemical Entities – medicines for human therapeutic use

Summary of delegates' final decisions

Substance	Final decision
Ocrelizumab	**Schedule 4 – New Entry** OCRELIZUMAB. Implementation date: **1 February 2017**
Eluxadoline	**Schedule 4 – New Entry** ELUXADOLINE. Implementation date: **1 February 2017**
Cobimetinib	**Schedule 4 – New Entry** COBIMETINIB. Implementation date: **1 February 2017**
Lenvatinib	**Schedule 4 – New Entry** LENVATINIB. Implementation date: **1 February 2017**
Talimogene laherparepvec	**Schedule 4 – New Entry** TALIMOGENE LAHERPAREPVEC. Implementation date: **1 February 2017**
Dermatophagoides pteronyssinus and *Dermatophagoides farinae* extract	**Schedule 4 – New Entry** DERMATOPHAGOIDES PTERONYSSINUS AND DERMATOPHAGOIDES FARINAE EXTRACT. Implementation date: **1 February 2017**
Fomepizole	**Schedule 4 – New Entry** FOMEPIZOLE. Implementation date: **1 February 2017**
Sarilumab	**Schedule 4 – New Entry** SARILUMAB. Implementation date: **1 February 2017**

Osimertinib	**Schedule 4 – New Entry** OSIMERTINIB. Implementation date: **1 February 2017**
Lipegfilgrastim	**Schedule 4 – New Entry** LIPEGFILGRASTIM. Implementation date: **1 February 2017**
Elotuzumab	**Schedule 4 – New Entry** ELOTUZUMAB. Implementation date: **1 February 2017**
Ixazomib	**Schedule 4 – New Entry** IXAZOMIB. Implementation date: **1 February 2017**
Lumacaftor	**Schedule 4 – New Entry** LUMACAFTOR. Implementation date: **1 February 2017**
Sodium zirconium cyclosilicate	**Schedule 4 – New Entry** SODIUM ZIRCONIUM CYCLOSILICATE. Implementation date: **1 February 2017**
Sonidegib	**Schedule 4 – New Entry** SONIDEGIB. Implementation date: **1 February 2017**
Venetoclax	**Schedule 4 – New Entry** VENETOCLAX. Implementation date: **1 February 2017**
Carfilzomib	**Schedule 4 – New Entry** CARFILZOMIB. Implementation date: **1 February 2017**

2.1 Ocrelizumab

Scheduling proposal

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

Substance summary

Ocrelizumab is a humanised monoclonal antibody designed to selectively target CD20-positive B cells, a specific type of immune cell thought to be a key contributor to myelin (nerve cell insulation and support) and axonal (nerve cell) damage.

Ocrelizumab is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity). Ocrelizumab is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed. The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Ocrelizumab is not specifically scheduled in the current Standard for the Uniform Scheduling of Medicines and Poisons.

Ocrelizumab is captured in the current Standard for the Uniform Scheduling of Medicines and Poisons under the following group entry:

Schedule 4

MONOCLONAL ANTIBODIES for therapeutic use **except**:

a) in diagnostic test kits; or

b) when separately specified in these Schedules.

International regulations

Ocrelizumab is not classified in New Zealand.

Delegate's consideration

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

- Subsection 52E(1) of the Therapeutic Goods Act 1989;
- The Scheduling Policy Framework (2015) scheduling factors; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include ocrelizumab in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

OCRELIZUMAB.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical experience in Australia.
- It is an immune suppressant and use of which will require regular monitoring.
- Strong and fairly specific immune suppressant for treatment of Multiple Sclerosis.
- It is a strong immune suppressant, requires intravenous infusion and observation following infusion to reduce adverse effects of any infusion reactions.
- Must be infused intravenously.

2.2 Eluxadoline

Scheduling proposal

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

Substance summary

Eluxadoline is a locally acting, mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist. Eluxadoline is also an agonist at the kappa opioid receptor (κOR). The binding affinities (Ki) of eluxadoline for human μOR and δOR are 1.8 nM and 430 nM, respectively. The Ki of eluxadoline for human κOR has not been determined; however, the Ki for guinea pig cerebellum κOR is 55 nM. In animals, eluxadoline interacts with opioid receptors in the gut. Eluxadoline has demonstrated efficacy in normalising GI transit and defecation in several models of stress induced or post GI inflammation-altered GI function in animals. Eluxadoline has very low oral bioavailability and exerts no detectable central nervous system (CNS)-mediated effects when administered orally to animals at effective doses. Eluxadoline also reverses hyperalgesic responses in an animal model of acute colitis-induced visceral pain.

Eluxadoline is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

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

Scheduling status

Eluxadoline is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Eluxadoline is not classified in New Zealand.

Delegate's consideration

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989;*
- The Scheduling Policy Framework (2015) scheduling factors; and

- The new drug application;

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include eluxadoline in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

ELUXADOLINE.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical/marketing experience in Australia.
- It is intended for the treatment of a condition which requires medical assessment and monitoring.
- It has potential for misuse and abuse.
- Substance is an opioid agonist with very low levels of absorption from the gut. It is presented as an oral dose form and is intended to act locally within the gut. If injected eluxadoline has opioid effects on the CNS and therefore has abuse potential.

2.3 Cobimetinib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of cobimetinib, a NCE for a human therapeutic medicine.

Substance summary

Cobimetinib is a highly selective allosteric inhibitor that targets MEK1 and MEK2 tyrosine-threonine kinases. It has shown high inhibitory potency in biochemical and cell based assays, as well as broad anti-tumour activity *in vivo* in xenograft tumour models, including those that are mutated for BRAF and KRAS.

Cobimetinib is indicated for use in combination with vemurafenib for the treatment of patients with un-resectable or metastatic melanoma with BRAF V600 mutation.

AAN – Cobimetinib

Scheduling status

Cobimetinib is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Cobimetinib is not classified in New Zealand.

Delegate's consideration

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

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include cobimetinib in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

COBIMETINIB.

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

The delegate decided that the reasons for the final decision comprise the following:

- Benefit/risk balance is considered positive for the approved use, but there is limited clinical experience with the product in Australia;
- cobimetinib is indicated for use in combination with vemurafenib for the treatment of patients with un-resectable or metastatic melanoma with BRAF V600 mutation;
- Toxicity was considered in TGA review of initial application and is addressed under benefit/risk balance above;
- The dosage, formulation, labelling, packaging and presentation were considered satisfactory in a TGA review of the initial application; and
- The potential for abuse was considered to be nil by the TGA when reviewing the initial application.

2.4 Lenvatinib

Scheduling proposal

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

Substance summary

Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including

fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

Lenvatinib is indicated for the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer.

AAN – Lenvatinib

Scheduling status

Lenvatinib is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Lenvatinib is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989;*
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include lenvatinib in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

LENVATINIB.

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

The delegate decided that the reasons for the final decision comprise the following:

- Benefit/risk balance is considered positive for the approved use, but there is limited clinical experience with the product in Australia;
- Lenvatinib is indicated for the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer;
- Toxicity was considered in TGA review of initial application and is addressed under benefit/risk balance above;
- The dosage, formulation, labelling, packaging and presentation were considered satisfactory in the TGA review of the initial application; and
- The potential for abuse was considered to be nil in a TGA review of the initial application.

2.5 Talimogene laherparepvec

Scheduling proposal

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

Substance summary

Talimogene laherparepvec is a modified herpes simplex virus type 1 (HSV-1) encoding GM-CSF.

Talimogene laherparepvec is indicated for the treatment of melanoma that is regionally or distantly metastatic.

ABN – Talimogene laherparepvec

Scheduling status

Talimogene laherparepvec is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Talimogene laherparepvec is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines;
- The new drug application; and
- Other [OGTR reports].

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include talimogene laherparepvec in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

TALIMOGENE LAHERPAREPVEC.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse; and (f) any other matters that the Secretary considers necessary to protect public health.

The delegate decided that the reasons for the final decision comprise the following:

- Benefit/risk balance is considered positive for the approved use, but there is limited clinical experience with the product in Australia;
- talimogene laherparepvec is indicated as monotherapy for the treatment of melanoma in patients with unresectable cutaneous, subcutaneous or nodal lesions after initial surgery;
- Toxicity was considered in TGA review of initial application and is addressed under benefit/risk balance above;
- Dosage, formulation, labelling, packaging and presentation were considered satisfactory in a TGA review of the initial application;
- The potential for abuse was considered to be nil in a TGA review of the initial application;
- Environmental/person-to-person spread considered under benefit/risk balance above.

2.6 Dermatophagoides pteronyssinus and Dermatophagoides farinae extract

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract (American & European house dust mites (HDM) extract), a NCE for a human therapeutic medicine.

Substance summary

Dermatophagoides pteronyssinus and *Dermatophagoides farinae* extract (American & European HDM extract) is a standardised allergen extract (50%) of the American HDM and the European HDM species, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

In patients with a positive test of house dust mite sensitisation (skin prick test and/or specific IgE), *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract is indicated for the treatment of moderate to severe HDM-allergic rhinitis despite use of symptom-relieving medication, and HDM-allergic asthma not responsive to inhaled corticosteroids in adults.

ABN – American house dust mite extract

ABN – European house dust mite extract

Scheduling status

Dermatophagoides pteronyssinus and *Dermatophagoides farinae* extract is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Dermatophagoides pteronyssinus and *Dermatophagoides farinae* extract is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision, hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;

- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

DERMATOPHAGOIDES PTERONYSSINUS AND DERMATOPHAGOIDES FARINAE EXTRACT.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose and the extent of use of a substance; (c) the toxicity of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The delegate decided that the reasons for the final decision comprise the following:

- It is a NCE with no clinical experience in Australia.
- *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract is indicated for the treatment of adults diagnosed with:
  - HDM allergic rhinitis not well controlled despite use of symptom relieving medication; or
  - HDM allergic asthma not well controlled by inhaled corticosteroids;
- When treated with *D. pteronyssinus* and *D. farinae* extract the patient is exposed to the allergen that causes the allergic symptoms. Therefore local allergic reactions are to be expected during the treatment period. The use of anti-allergic medication (e.g. antihistamines) should be considered for any potential significant local adverse reactions to the *D. pteronyssinus* and *D. farinae* extract;
- Need a medical doctor to prescribe to the right patient group; and
- *D. pteronyssinus* and *D. farinae* extract is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population.

2.7 Fomepizole

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of fomepizole, a NCE for a human therapeutic medicine.

Substance summary

Fomepizole is an alcohol dehydrogenase inhibitor for the treatment of methanol and ethylene glycol poisoning and acts to inhibit the breakdown of these toxins into their active toxic metabolites.

Fomepizole is indicated for the treatment of methanol or ethylene glycol poisoning.

Table 2.7: Properties, identifiers and naming of fomepizole

Property	Fomepizole
CAS Number	7554-65-6
Chemical formula	$C_4H_6N_2$
Molecular weight	82.11 g/mol
Chemical name/s	4-methyl-1*H*-pyrazole; 4-methylpyrazole
AAN	Fomepizole

Scheduling status

Fomepizole is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Fomepizole is on the World Health Organization (WHO) Model List of Essential Medicines as an essential medicine for priority diseases.

Fomepizole is available as a prescription only drug in the USA, Canada and New Zealand.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines (ACPM); and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include fomepizole in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

FOMEPIZOLE.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical experience in Australia;
- The risks and benefits of the medicine have been considered and are outlined in the Product Information, Delegate's Request for ACPM advice and the TGA evaluation reports;
- Fomepizole is indicated as an antidote for the treatment of ethylene glycol or methanol poisoning;
- It has no previous experience of use in Australia but has been approved for many years overseas;
- It is proposed for use in hospitals;
- Fomepizole is a competitive inhibitor of alcohol dehydrogenase;
- The medicine has risks that may require medical intervention, evaluation and monitoring by a medical practitioner;
- Labelling needs to comply with the requirements for a prescription only medicine; and
- It does not appear to produce dependency and the abuse potential appears to be low.

2.8 Sarilumab

Scheduling proposal

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

Substance summary

Sarilumab is a fully human monoclonal antibody targeting interleukin-6 receptor alpha (IL-6Rα).

Sarilumab, in combination with non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs), is indicated for the treatment of moderate to severe Rheumatoid Arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs.

ABN – Sarilumab

Scheduling status

Sarilumab is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Sarilumab is not classified in New Zealand, Canada or the USA.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;

- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include sarilumab in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

SARILUMAB.

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

The delegate decided that the reasons for the final decision comprise the following:

- Sarilumab is a new biological entity with no clinical experience in Australia;
- Sarilumab is a fully human monoclonal antibody targeting interleukin-6 receptor alpha (IL-6Rα);
- Sarilumab, in combination with non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs), is indicated for the treatment of moderate to severe Rheumatoid Arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs;
- Sarilumab is proposed for use in the hospital and community;
- Sarilumab has risks that require medical intervention, evaluation and monitoring by a medical practitioner experienced in the diagnosis and treatment of rheumatoid arthritis and use of biological medicines; and
- The labeling of sarilumab needs to comply with the requirements for a prescription only medicine.

2.9 Osimertinib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of osimertinib, a NCE for a human therapeutic medicine.

Substance summary

For the delegate to consider the scheduling of the NCE, osimertinib.

Osimertinib is an irreversible inhibitor of mutant forms of epidermal growth factor receptor (EGFR) found in non-small cell lung cancer (NSCLC).

Osimertinib is indicated for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer.

AAN – Osimertinib

Scheduling status

Osimertinib is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Osimertinib is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision, hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include osimertinib in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

OSIMERTINIB.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with limited clinical experience in Australia;
- The conclusion of the TGA evaluation was that a positive benefit / risk balance exists in the specified target population;
- Osimertinib is indicated for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer; and
- The potential for abuse of osimertinib is unlikely.

2.10 Lipegfilgrastim

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration for the scheduling of lipegfilgrastim, a NCE for a human therapeutic medicine.

Substance summary

Lipegfilgrastim is a long-acting covalent conjugate of filgrastim[1] with methoxy polyethylene glycol (PEG) via a carbohydrate linker.

Lipegfilgrastim is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infection, as manifested by febrile neutropenia.

AAN – Lipegfilgrastim

Scheduling status

Lipegfilgrastim is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Lipegfilgrastim is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include lipegfilgrastim in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

LIPEGFILGRASTIM.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a NCE with no clinical/marketing experience in Australia;

[1] Filgrastim [recombinant methionyl human granulocyte-colony stimulating factor [G-CSF]] is produced in Escherichia coli cells by recombinant DNA technology

- the condition being treated (neutropenia or febrile neutropenia) necessitates an appropriate diagnosis for the use of this medicine, and for ongoing patient management and monitoring, by a medical professional; and
- The potential for abuse of lipegfilgrastim is unlikely.

2.11 Elotuzumab

Scheduling proposal

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

Substance summary

Elotuzumab is a humanised, IgG1 monoclonal antibody (mab) that specifically binds to human Signalling Lymphocyte Activation molecule family member 7 (SLAMF7) proteins. It consists of the complimentary determining regions of the parent mouse antibody, MuLuc63, grafted onto human IgG1 heavy chain and kappa light chain regions. SLAMF7 is highly expressed in MM cells independent of diseases stage or cytogenetic abnormalities. SLAMF7 is also expressed on natural killer (NK) cells, natural killer T cells (NKT), plasma cells and on specific immune subsets (CD8+T and CD4+ T cells) but is not detected on hematopoietic stem cells or on most normal tissues. Binding of elotuzumab to NK cells directly activates immune cells through both the SLAMF7 and CD16 pathways enhancing anti-myeloma activity in vitro. Elotuzumab also binds to the SLAMF7 protein on myeloma cells and facilitates the interaction of NK cells with myeloma cells to mediate the killing of these malignant cells through antibody-dependent cellular cytotoxicity (ADCC). In preclinical models, elotuzumab has single-agent anti-MM activity and can synergize with lenalidomide and bortezomib to further enhance this activity.

Elotuzumab is indicated as a combination therapy for the treatment of multiple myeloma in adult patients who have received one or more prior therapies.

AAN – Elotuzumab

Scheduling status

Elotuzumab is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Elotuzumab is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include elotuzumab in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

ELOTUZUMAB.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; and (b) the purpose and the extent of use of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- It is a NCE with no clinical/marketing experience in Australia;
- Elotuzumab has risks of infections, second primary malignancies, hepatotoxicity and infusion related reactions;
- Treatment should be initiated and supervised by physicians experienced in the treatment of multiple myeloma;
- Elotuzumab is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy; and
- The potential for abuse of elotuzumab is unlikely.

2.12 Ixazomib

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of ixazomib (as citrate), a NCE for a human therapeutic medicine.

Substance summary

Ixazomib (as citrate) is a 20S proteasome inhibitor for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy. It is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

AAN – Ixazomib/ixazomib citrate

Scheduling status

Ixazomib (as citrate) is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Ixazomib (as citrate) is not classified in New Zealand.

Delegate's consideration

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

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include ixazomib in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

IXAZOMIB.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; and (b) the purpose and the extent of use of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- It is a NCE with no clinical/marketing experience in Australia;
- Ixazomib has risks of neuropathy, infections, neutropaenia and thrombocytopaenia;
- Treatment should be initiated and supervised by physicians experienced in the treatment of multiple myeloma;
- Ixazomib is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy; and
- The potential for abuse of ixazomib is unlikely.

2.13 Lumacaftor

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of lumacaftor, a NCE for a human therapeutic medicine.

Substance summary

Lumacaftor is a selective CFTR corrector that acts on F508del-CFTR to increase the amount of functional CFTR at the cell surface to enhance chloride transport. Lumacaftor acts on CFTR to facilitate the cellular processing and trafficking of CFTR, allowing the protein to reach the cell surface, where it exhibits improved chloride channel function compared to uncorrected F508del-CFTR. F508del-CFTR that has been delivered to the cell surface by lumacaftor can be further potentiated by ivacaftor. Lumacaftor can increase the amount of normal CFTR at the cell surface and can correct certain other CFTR forms, including certain mutations that cause defects in processing. Ivacaftor has been shown to have CFTR potentiator properties.

Lumacaftor is a component of the FDC product ORKAMBI (lumacaftor/ivacaftor), which is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

AAN – Lumacaftor.

Scheduling status

Lumacaftor is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Lumacaftor is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision, hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include lumacaftor in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

LUMACAFTOR.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a NCE with no clinical/marketing experience in Australia; and
- The potential for abuse of lumacaftor is unlikely.

2.14 Sodium zirconium cyclosilicate

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of sodium zirconium cyclosilicate, a NCE for a human therapeutic medicine.

Substance summary

Sodium zirconium cyclosilicate is a highly selective cation exchanger that entraps potassium in the intestinal tract in exchange for sodium and hydrogen.

Sodium zirconium cyclosilicate is indicated for the treatment of hyperkalaemia in adult patients.

AAN – sodium zirconium cyclosilicate

Scheduling status

Sodium zirconium cyclosilicate is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Sodium zirconium cyclosilicate is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include sodium zirconium cyclosilicate in Schedule 4, with an implementation date of **1 February 2017.**

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

SODIUM ZIRCONIUM CYCLOSILICATE.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a NCE with no clinical/marketing experience in Australia;
- The intended use is the treatment of hyperkaelemia;
- This medicine is not absorbed, it acts locally in the gastrointestinal tract; and
- The potential for abuse of sodium zirconium cyclosilicate is unlikely.

2.15 Sonidegib

Scheduling proposal

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

Substance summary

Sonidegib diphosphate is a potent, selective, and orally bioavailable smoothened (Smo) antagonist. Smoothened is a transmembrane G protein-coupled receptor-like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway.

Sonidegib diphosphate is indicated for the treatment of adult patients with:

- Locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.
- Metastatic BCC.

AAN – Sonidegib diphosphate

Scheduling status

Sonidegib diphosphate is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Sonidegib diphosphate is not classified in New Zealand.

Delegate's consideration

The delegate made a delegate-only decision; hence the Advisory Committee on Medicines Scheduling was not consulted.

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include sonidegib in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

SONIDEGIB.

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

The delegate decided that the reasons for the final decision comprise the following:

- It is a NCE with no clinical experience in Australia;

- Sonidegib is Pregnancy Category X (as is the first in class Vismodegib) but its use is in a restricted population and likely to be under close supervision of appropriately specialized physicians, therefore label warnings are not considered necessary at this stage; and
- The potential for abuse of sonidegib is unlikely.

2.16 Venetoclax

Scheduling proposal

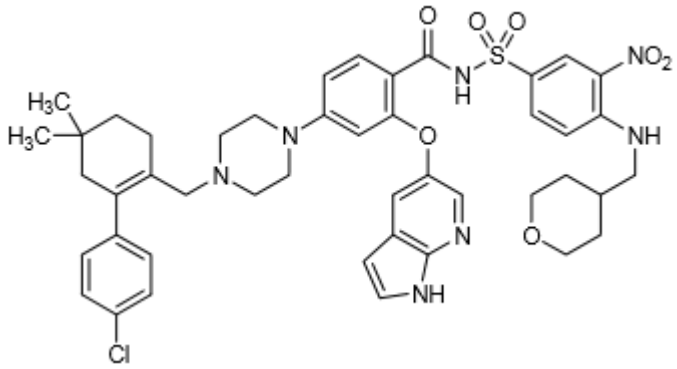
The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of venetoclax, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Venetoclax is a BH#-mimetic which acts as a B-cell lymphoma 2 (Bcl-2) inhibitor, blocking the anti-apoptotic Bcl-2 protein. This leads to programmed cell death of chronic lymphocytic leukemia (CCL) cells.

Venetoclax is indicated for patients with relapsed/refractory chronic lymphocytic leukaemia with 17p deletion and for patients without 17p deletion who have no other suitable treatment options.

Table 2.16: Identifiers, properties and naming of Venetoclax

Property	Venetoclax
CAS Number	1257044-40-8
Chemical structure	
Molecular formula	$C_{45}H_{50}ClN_7O_7S$
Molecular weight	868.44 g/mol
Chemical name/s	4-{4-{[2-(4-Chlorophenyl)-4,4-dimethyl-1-cyclohexen-1-yl]methyl}-1-piperazinyl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide (IUPAC)
ANN/INN	Venetoclax (ANN and INN)

Scheduling status

Venetoclax is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Venetoclax is unclassified in New Zealand.

Venetoclax is a prescription medicine in Canada and the United States of America.

Delegate's consideration

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

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include Venetoclax in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

VENETOCLAX.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; and (c) the toxicity of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- Venetoclax is an NCE with no clinical or marketing experience in Australia.
- Venetoclax is indicated for patients with relapsed/refractory chronic lymphocytic leukaemia with 17p deletion and for patients without 17p deletion who have no other suitable treatment options.
- Venetoclax has reported risks of tumour lysis syndrome, neutropaenia, thrombocytpaenia, diarrhea, nausea, infections, autoimmune haemolytic anaemia and immune thryombocytopaenic purpura.
- The potential for abuse of Venetoclax is unlikely.

2.17 Carfilzomib

Scheduling proposal

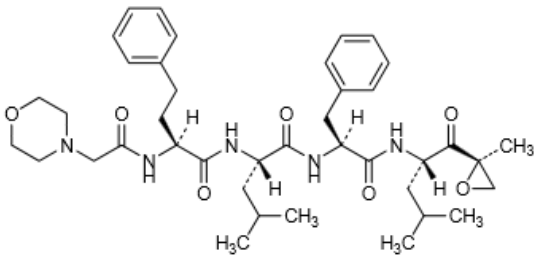
The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of carfilzomib, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Carfilzomib is an anti-cancer drug acting as a selective tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the *N*- terminal threonine-containing actives sites of the 20S proteasome (the proteolytic core particle within the 26S proteasome). It has anti-proliferative and pro-apoptotic activities *in vitro* in solid and haematologic tumour cells. In animals, Carfilzomib inhibits proteasome activity in blood and tissue and delays tumour growth in models of multiple myeloma, haematologic, and solid tumours.

Carfilzomib is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Table 2.17: Identifiers, properties and naming of Carfilzomib

Property	Carfilzomib
CAS Number	868540-17-4
Chemical structure	
Molecular formula	$C_{40}H_{57}N_5O_7$
Molecular weight	719.91 g/mol
Chemical name/s	(2*S*)-4-Methyl-N-[(2*S*)-1-[[(2*S*)-4-methyl-1-[(2*R*)-2-methyloxiran-2-yl]-1-oxopentan-2-yl]amino]-1-oxo-3-phenylpropan-2-yl]-2-[[(2*S*)-2-[(2-morpholin-4-ylacetyl)amino]-4-phenylbutanoyl]amino]pentanamide (IUPAC)
ANN/INN	Carfilzomib (ANN and INN)

Scheduling status

Carfilzomib is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Carfilzomib in unclassified in New Zealand and Canada.

Carfilzomib is a prescription medicine in the United States of America.

Delegate's consideration

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

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

- Subsection 52E(1) of the *Therapeutic Goods Act 1989;*
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application

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

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include Carfilzomib in Schedule 4, with an implementation date of **1 February 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

CARFILZOMIB.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- Carfilzomib is an NCE with no clinical/marketing experience in Australia.
- Carfilzomib is indicated for the treatment of relapsed/refractory multiple myeloma.
- Carfilzomib has reported adverse events of pulmonary toxicity, pulmonary hypertension, hypertension, tumour lysis syndrome, haemorrhage and thrombocytopaenia, venous thrombosis, hepatic toxicity and posterior reversible encephalopathy syndrome.
- Carfilzomib is administered intravenously, and has a complex administration schedule.
- The potential for abuse of Carfilzomib is unlikely.