



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

29 June 2017

(ACMS and ACCS meetings – March 2017)

## Notice under subsections 42ZCZS/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/42ZCZX of 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 initially referred to the March 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS#20);
- scheduling proposals initially referred to the March 2017 Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS#15);
- scheduling proposals initially referred to the March 2017 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#19); and
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

## Scheduling proposals referred to the expert advisory committees.

### Pre-meeting public notices

On [22 December 2016](#) and [3 February 2017](#), under subsection 42ZCZK of the *Therapeutic Goods Regulations 1990* (the Regulations), the delegate published pre-meeting public notices on the TGA website which specified the proposed amendments to the current Poisons Standard. The notices also invited public comment on the scheduling proposals referred to the expert advisory committees.

The pre-meeting consultation periods were open for public comment for 20 business days and closed on 10 February 2017 and 3 March 2017, respectively.

In accordance with subsection 42ZCZL of the Regulations, redacted versions of public submissions received in response to these invitations for public comment will be published on or after the date of this notice on the TGA website at [Public submissions on scheduling matters](#).

## Interim decisions

On 17 May 2017, in accordance with subsection 42ZCZN of the Regulations, the delegate made an interim decision on an application and under subsection 42ZCZP of the Regulations, [the interim decision](#) and the reasons for the decision was published on TGA website. Further submissions were also invited from the applicants and parties who made valid pre-meeting submissions. The invitation to make submissions was open for 10 business days and closed on 31 May 2017.

Redacted versions of public submissions will be published at [Public submissions on scheduling matters](#) on or after the date of this notice.

## Final decisions

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

## Matters not referred to an advisory committee

According to subsections 42ZCZT/42ZCZU of the Regulations 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 FRL, is available at [SUSMP](#).

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# Part A - Final decisions on matters referred to an expert advisory committee (March 2017)

## 1. Advisory Committee on Medicines Scheduling (ACMS #20)

### Summary of final interim decisions

The implementation date for the following decisions is **1 October 2017** unless otherwise indicated.

Substance	Final decision
Dihydrocodeine	<p><b>Schedule 8 – Amend Entry</b></p> <p>DIHYDROCODEINE <b>except</b> when included in Schedule 3 or 4.</p> <p><b>Schedule 4 – Amend Entry</b></p> <p>DIHYDROCODEINE when compounded with one or more other therapeutically active substances:</p> <ul style="list-style-type: none"> <li>a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or</li> <li>b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine,</li> </ul> <p><b>except</b> when included in Schedule 3.</p> <p><b>Schedule 3 – Amend Entry</b></p> <p>DIHYDROCODEINE when indicated for cough suppression and compounded with one or more other therapeutically active substances:</p> <ul style="list-style-type: none"> <li>a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or</li> <li>b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine.</li> </ul> <p><b>Schedule 2 – Delete Entry</b></p>
1,3-Dimethylbutylamine (DMBA) and other aliphatic alkylamines including 1,5-dimethylhexylamine (DMHA)	<p><b>Schedule 10 – New Entries</b></p> <p>1,3-DIMETHYLBUTYLAMINE (DMBA) <b>except</b> when separately specified in these schedules.</p> <p>1,5-DIMETHYLHEXYLAMINE (DMHA) <b>except</b> when separately specified in these schedules.</p> <p>ALKYLAMINES WITH STIMULANT PROPERTIES <b>except</b> when separately specified in these schedules.</p> <p><b>Index – New Entries</b></p>

Substance	Final decision
	<p><b>1,3-DIMETHYLBUTYLAMINE (DMBA)</b> cross reference: octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)  Schedule 10</p> <p><b>1,5-DIMETHYLHEXYLAMINE (DMHA)</b> cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)  Schedule 10</p> <p><b>ALKYLAMINES WITH STIMULANT PROPERTIES</b> cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate)  Schedule 10</p>
Ulipristal	<p><b>Schedule 3</b>  ULIPRISTAL for emergency post-coital contraception.</p> <p><b>Appendix H – New Entry</b>  ULIPRISTAL for emergency post-coital contraception</p> <p><b>Index – Amend Entry</b>  <b>ULIPRISTAL</b>  Schedule 4 Schedule 3 Appendix H  <i>The implementation date is <b>1 February 2018</b>.</i></p>
Ibuprofen	<p><b>Schedule 3 – Amend Entry</b>  IBUPROFEN:</p> <ul style="list-style-type: none"> <li>a) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units, when labelled: <ul style="list-style-type: none"> <li>i) with a recommended daily dose of 1200 mg or less of ibuprofen; and</li> <li>ii) not for the treatment of children under 12 years of age; or</li> </ul> </li> <li>b) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32</li> </ul>

Substance	Final decision
	<p>dosage units, when labelled:</p> <ul style="list-style-type: none"> <li>i) with a recommended daily dose of 1200 mg or less of ibuprofen; and</li> <li>ii) not for the treatment of children under 12 years of age,</li> </ul> <p><b>except</b> when included in or expressly excluded from Schedule 2.</p> <p><b>Appendix H – New Entry</b></p> <p>IBUPROFEN</p>
Flurbiprofen	<p>The delegate's final decision is that the current scheduling of flurbiprofen remains appropriate.</p>
Penciclovir	<p><b>Schedule 4 – Amend Entry</b></p> <p>PENCICLOVIR <b>except</b> in preparations containing 1 per cent or less of penciclovir for the treatment of <i>herpes labialis</i> in packs containing 10 g or less.</p> <p><b>Schedule 2 – Delete Entry</b></p> <p><b>Index – Amend Entry</b></p> <p><b>PENCICLOVIR</b></p> <p>Schedule 4</p>
Loratadine	<p><b>Schedule 4 – Amend Entry</b></p> <p>LORATADINE <b>except</b>:</p> <ul style="list-style-type: none"> <li>a) when included in Schedule 2; or</li> <li>b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and over, when: <ul style="list-style-type: none"> <li>i) in a primary pack containing 10 dosage units or less; and</li> <li>ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.</li> </ul> </li> </ul> <p><b>Schedule 2 – Amend Entry</b></p> <p>LORATADINE in preparations for oral use <b>except</b> in divided preparations for the treatment of seasonal allergic rhinitis when:</p> <ul style="list-style-type: none"> <li>a) in a primary pack containing 10 dosage units or less when labelled for adults and children 6 years and over; and</li> <li>b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.</li> </ul>

## 1.1. Dihydrocodeine

### *Referred scheduling proposal*

A delegate from the TGA has referred the substance dihydrocodeine for consideration for the appropriateness of the Schedule 2 and Schedule 3 entries, noting the recent up-scheduling of codeine.

### *Current scheduling status*

Dihydrocodeine is currently listed in Schedules 8, 4, 3 and 2 of the Poisons Standard as follows:

#### **Schedule 8**

DIHYDROCODEINE **except** when included in Schedule 2, 3 or 4.

#### **Schedule 4**

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or
- b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine,

**except** when included in Schedule 2 or 3.

#### **Schedule 3**

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or
- b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine,

**except** when included in Schedule 2.

#### **Schedule 2**

DIHYDROCODEINE when compounded with aspirin and no other therapeutically active substance in divided preparations:

- a) containing 5 mg or less of dihydrocodeine per dosage unit;
- b) packed in blister or strip packaging or in a container with a child-resistant closure;
- c) enclosed in primary packs containing 25 or less dosage units; and
- d) labelled with a recommended dose not exceeding 10 mg of dihydrocodeine.

The related substance acetyldihydrocodeine is in Schedule 8.

### *Scheduling history*

In December 2016, the delegate made a decision to up-schedule codeine from Schedules 2 and 3 to Schedule 4. The [decision and reasons](#) are on the TGA website.

In November 1979 – June 1980, the Poisons Schedule Committee (PSC) reviewed the scheduling of dihydrocodeine in certain preparations following evidence of abuse. The committee discussed the desirability of placing uncompounded preparations containing less than 1% dihydrocodeine in Schedule 4, and considered that uncompounded preparations currently available in Schedule 2 should



be classified in Schedule 8. Two manufacturers sought the committee's concurrence that inclusion of sorbitol (40 g/100 mL) in their products would remove the need for Schedule 2 status of their products. Members agreed to take no further action.

Between August 1985 and July 1987, the PSC and Drugs and Poisons Schedule Committee (DPSC) reviewed the scheduling of dihydrocodeine, following potency concerns raised by WA regarding the inclusion of dihydrocodeine tartrate in Schedule 2 as this allowed a higher limit than codeine, which was reported to be equipotent. At the November 1986 meeting the committee foreshadowed a recommendation to alter the Schedule 2 entries for opiates (except dihydrocodeine) and other substances with regard to a specific quantity per dosage unit in divided preparations, a percentage limit for undivided preparations and an upper dose limit recommended for both divided and undivided preparations. Members agreed to delete dihydrocodeine from Schedule 2 and enter it into Schedule 3 in February 1987. Following this, the committee received further information about the decision to delete Schedule 2 and create a new Schedule 3 entry. The committee noted a potency equivalence of 5 mg dihydrocodeine to 10 mg of codeine and agreed to a new Schedule 2 entry for dihydrocodeine. A new Schedule 2 entry was also made for dihydrocodeine when in combination with aspirin.

In April 1994, the National Drugs and Poisons Scheduling Committee (NDPSC) considered a request from the Australian Pharmaceutical Advisory Council (APAC) to review the scheduling of dihydrocodeine combined with paracetamol, in view of the fact that dihydrocodeine with aspirin is Schedule 2. Members were not aware of a registered OTC product containing paracetamol and dihydrocodeine or of a detailed technical submission supporting such a change, or was there any response to the Gazetted invitation for public comment. Accordingly the committee was unable to accede to the request.

In June 2010 – September 2011, the NDPSC and ACMS, considered a TGA request to reschedule several medicines, following a TGA review of the safety, efficacy, availability and packaging of all OTC cough and cold medicines. The review concluded that there was a lack of evidence of efficacy and potential safety concerns associated with use in children, especially those aged less than 6 years, and stated that the current scheduling of codeine, dihydrocodeine and pseudoephedrine was appropriate. Members noted that, of the 22 substances identified in the TGA review, a number were recommended for exemption from the proposed cascade as it was considered that either existing controls were sufficient (codeine, dihydrocodeine and pseudoephedrine) or that scheduling was not necessary (ammonia). Members noted that for some substances the current scheduling may in fact be more restrictive than the proposed cascade (e.g., pseudoephedrine) as this was the basis for the TGA Panel recommending that existing controls were sufficient for codeine, dihydrocodeine and pseudoephedrine and did not need to be rescheduled. The committee agreed that the use of certain substances in preparations for treating cough and cold be rescheduled to:

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

However, the delegate decided that the scheduling of dihydrocodeine and another 14 substances (including codeine) in cough and cold preparations remained appropriate.

### ***Scheduling application***

This was a delegate initiated application made in response to the scheduling changes of codeine where from 1 February 2018, the Schedule 2 and 3 entries for codeine will be deleted.

### ***Australian regulatory information***

There are currently 7 ARTG products containing dihydrocodeine tartrate that are included on the ARTG.

## ***International regulations***

### *Japan*

In Japan, dihydrocodeine is available without a prescription; used in cough medicines. Medicines in Japan containing dihydrocodeine are combined with caffeine to offset the sedative effects and discourage recreational use. Sale is limited by quantity and restricted by age.

### *UK*

In the UK and other countries, 30 mg tablets containing only dihydrocodeine as the active ingredient are available; 40 mg dihydrocodeine tablets are also available in the UK. Dihydrocodeine is considered to be a Class B drug in the UK, but is available OTC in small amounts (less than 8 mg), when combined with paracetamol.

Dihydrocodeine is listed in Schedule 5 of the Misuse of Drugs Regulations 2001, exempting it from prohibition of possession provided that it is in the form of a single preparation not designed for injection and less than 100 mg (as free base) or with a total concentration less than 2.5% (as free base).

### *New Zealand*

The NZ database of Medicine Classifications states that dihydrocodeine (or drocode) is a prescription medicine.<sup>1</sup> It is also conditionally classed as a C2 and C6 Controlled drug (drugs that pose a moderate risk of harm to individuals, or to society, by its misuse):<sup>2</sup>

Acetyldihydrocodeine is also a Class C2 controlled drug in NZ.

### *United States of America*

In the USA, dihydrocodeine is a Schedule II controlled substance.

Preparations containing small amounts of dihydrocodeine are classified as Schedule III or V, depending on the concentration of dihydrocodeine relative to other active constituents, such as paracetamol (acetaminophen). The USA currently has 2 combination products registered and available as prescription medicines containing paracetamol (acetaminophen) or aspirin with caffeine and dihydrocodeine tartrate (dihydrocodeine bitartrate).<sup>3</sup>

## ***Substance summary***

Dihydrocodeine (CAS number 125-28-0) is a semi-synthetic phenanthrene opioid receptor agonist analgesic with a molecular weight of 301.4,  $C_{18}H_{23}NO_3$  (molecular weight for the tartrate is 451.5, molecular formula  $C_{22}H_{29}NO_9$ , CAS number for the tartrate is 5965-13-9). Dihydrocodeine is a chemical derivative of codeine and is an opioid pain reliever that produces similar effects to codeine, prepared by codeine or neopine (Merck Index). The chemical name for dihydrocodeine is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol. Dihydrocodeine is a white or almost white, crystalline powder, freely soluble in water, sparingly soluble in alcohol and practically insoluble in cyclohexane. Martindale<sup>4</sup>, indicates that dihydrocodeine is available as both tartrate and phosphate salts.

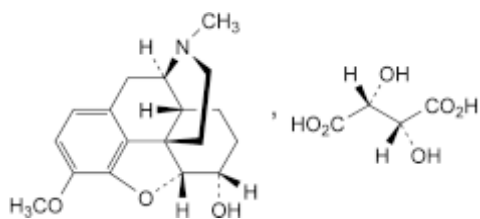
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<sup>1</sup> [Database of Medicine Classifications](#)

<sup>2</sup> [Misuse of Drugs Act 1975: Schedule 3 Class C controlled drugs](#)

<sup>3</sup> [Drugs@FDA: FDA Approved Drug Products](#)

<sup>4</sup> [Dihydrocodeine](#)



**Figure 1.1: Structure of dihydrocodeine tartrate**

### *Abuse*

As with other opioids, tolerance and physical and psychological dependence develop with repeated use of dihydrocodeine. Martindale indicates that dihydrocodeine has been reported to be widely abused by opiate addicts.<sup>5</sup>

### *Pharmacokinetics*

Dihydrocodeine is converted by cytochrome P450 isoenzyme CYP2D6 in the liver to the primary active metabolite dihydromorphine<sup>6</sup>. Oral bioavailability is approximately 20%. Dihydromorphine has potent analgesic activity, although the analgesic effect of dihydrocodeine appears to be mainly due to the parent compound. Dihydrocodeine is excreted in urine as unchanged drug and metabolites, including glucuronide conjugates. Elimination half-life ranges from 3.5 - 5 h. Martindale reports that the peak plasma concentration for dihydrocodeine is delayed and the area under the plasma concentration-time curve is greater in subjects with renal impairment compared with healthy subjects.

### ***Pre-meeting public submissions***

Five (5) public submissions were received.

*Three (3) submissions supported the scheduling proposal. The main points were:*

- Cases of misuse/abuse of dihydrocodeine reported to the NSW Poisons Information Centre have increased in recent years.
- Acknowledge no reason to have different scheduling compared with codeine, but also supports deleting Schedule 2 and amending Schedule 3 and Schedule 4 pack sizes.

*Two (2) submissions did not support the scheduling proposal. The main points were:*

- Schedule 3 is appropriate for dihydrocodeine in low doses when indicated as a cough suppressant. There have been no reported events related to abuse or dependence of OTC dihydrocodeine products on the ARTG in the past 6 years. Undivided preparations of dihydrocodeine in conjunction with sorbitol are not seen as candidates for abuse or misuse.
- An additional safety measure of a mandatory warning label about the potential for addiction was proposed as an alternative.
- As there are no products on the ARTG containing any aspirin or other analgesic preparation co-formulated with dihydrocodeine for the treatment of pain, there is no opposition to the removal of dihydrocodeine from Schedule 2 of the SUSMP.

<sup>5</sup> Swadi H, *et al.* [Misuse of dihydrocodeine tartrate \(DF 118\) among opiate addicts](#). *BMJ* 1990; **300**: 1313; Robertson JR, *et al.* [Misuse of dihydrocodeine tartrate \(DF 118\) among opiate addicts](#). *BMJ* 1990; **301**: 119; Strang J, *et al.* [Misuse of dihydrocodeine tartrate \(DF 118\) among opiate addicts](#). *BMJ* 1990; **301**: 119; Seymour A, *et al.* [The role of dihydrocodeine in causing death among drug users in the west of Scotland](#). *Scott Med J* 2001; **46**: 143-6

<sup>6</sup> [Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple oral dosing](#) Wilder-Smith CH, *et al.* [The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers](#). *Br J Clin Pharmacol* 1998; **45**: 575-81

- There are already control measures in place in the pharmacy for dispensing Schedule 3 medicines. There is also a longstanding status of Schedule 3 medicines for the treatment of cough. Removal of dihydrocodeine from Schedule 3 would limit the availability of treatment options for stubborn cough available without a prescription. This would necessitate the consumer visiting the doctor for a prescription. This provides an added cost to the consumer.
- Dihydrocodeine is an efficacious cough-suppressant.
- There are minimal side effects with dihydrocodeine.

The [public submissions](#) will be made available on the TGA website.

### ***Summary of ACMS advice to the delegate***

The committee advised that the Schedule 2 entry for dihydrocodeine be deleted and the Schedule 8, 4 and 3 entries be amended as follows:

#### **Schedule 8 – Amend Entry**

DIHYDROCODEINE **except** when included in Schedule ~~2~~, 3 or 4.

#### **Schedule 4 – Amend Entry**

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or
- b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine,

**except** when included in Schedule ~~2~~ or 3.

#### **Schedule 3 – Amend Entry**

DIHYDROCODEINE **when indicated for cough suppression and** compounded with one or more other therapeutically active substances:

- a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or
- b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine.

**except** when included in Schedule 2.

#### **Schedule 2 – Delete Entry**

~~DIHYDROCODEINE when compounded with aspirin and no other therapeutically active substance in divided preparations:~~

- ~~a) containing 5 mg or less of dihydrocodeine per dosage unit;~~
- ~~b) packed in blister or strip packaging or in a container with a child-resistant closure;~~
- ~~c) enclosed in primary packs containing 25 or less dosage units; and~~
- ~~d) labelled with a recommended dose not exceeding 10 mg of dihydrocodeine.~~

The committee also recommended an implementation date of **1 October 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be

used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- Dihydrocodeine is effective for stubborn, unproductive cough.
- Dihydrocodeine has a known potential for abuse, but misuse is uncommon with the current formulation, and overdose, although possible, doesn't appear to be common.
- There is a single product available which is indicated for stubborn, unproductive cough.
- There is limited evidence of respiratory depression in overdose, and potential toxicity in high doses. Reports of overdose were largely from the UK where dihydrocodeine is used in the context of addiction treatment, and the product used is in tablet form.
- Dihydrocodeine can produce euphoria and has a known potential for abuse. The potential for abuse is limited by the formulation, indication, Poisons Schedule and potential cost.
- Consideration should be given to monitoring adverse events and additional safeguards to prevent misuse in light of the changed access to non-prescription codeine from February 2018.
- There is a lack of evidence of abuse of the current product to justify removing it from Schedule 3, however the Schedule 3 entry should be limited to products used for cough suppression.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to delete the Schedule 2 entry for dihydrocodeine and amend the Schedule 8, 4 and 3 entries. The proposed Schedule entry is as follows:

#### **Schedule 8 – Amend Entry**

DIHYDROCODEINE **except** when included in Schedule 3 or 4.

#### **Schedule 4 – Amend Entry**

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or
- b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine,

**except** when included in Schedule 3.

### **Schedule 3 – Amend Entry**

DIHYDROCODEINE when indicated for cough suppression and compounded with one or more other therapeutically active substances:

- a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or
- b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine.

### **Schedule 2 – Delete Entry**

The proposed implementation date is **1 October 2017**.

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 a substance; (b) the purposes for which a substance is to be used 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 of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- There is data indicating dihydrocodeine is an efficacious cough suppressant.
- There are lower blood levels of its metabolites compared to codeine.
- Dihydrocodeine has a known potential for abuse, but misuse is uncommon with the current formulation, and overdose, although possible, doesn't appear to be common.
- There is a single Schedule 3 product available which is indicated for stubborn, unproductive cough.
- There is limited evidence of respiratory depression in overdose, and potential toxicity in high doses. Reports of overdose were largely from the UK where dihydrocodeine is used in the context of addiction treatment, and the product used is in tablet form.
- Dihydrocodeine can produce euphoria and has a known potential for abuse. The potential for abuse is limited by the formulation, indication, Poisons Schedule and potential cost.
- Consideration should be given to monitoring adverse events and additional safeguards to prevent misuse in light of the changed access to non-prescription codeine from February 2018.
- There is a lack of evidence of abuse of the current product to justify removing it from Schedule 3; however, the Schedule 3 entry should be limited to products used for cough suppression. Restricting its Schedule 3 indication to cough suppression only will restrict products and use.
- There needs to be consideration on whether a 200mL Schedule 3 product is appropriate.
- There are no Schedule 2 products on the ARTG.

### **Public submissions on the interim decision**

One (1) public submission was received that supported the delegate's interim decision for dihydrocodeine.

The main points were:

- There are 7 ARTG listings for dihydrocodeine products, 6 of them for a Schedule 8 medicine and one for a Schedule 3 listing indicated for a stubborn, unproductive cough. Continuing to have dihydrocodeine available as a Schedule 3 medicine will continue to benefit the general public.

- The current formulation of the Schedule 3 dihydrocodeine product listed on the ARTG limits potential abuse by exerting unwanted gastrointestinal side effects if the daily dose is exceeded.
- Dihydrocodeine safety is suitably managed by pharmacists, including determining any potential for misuse.

### ***Delegate's final decision***

The delegate notes the submission, which supported the interim decision and as no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to delete the Schedule 2 entry for dihydrocodeine and amend the Schedule 8, 4 and 3 entries. The implementation date is **1 October 2017**.

## **1.2. 1,3-Dimethylbutylamine (DMBA) and other aliphatic alkylamines including 1,5-dimethylhexylamine (DMHA)**

### ***Referred scheduling proposal***

An application was submitted to include entries for 1,3-dimethylbutylamine (DMBA) and other aliphatic alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10.

### ***Current scheduling status***

DMBA and DMHA are currently not specifically scheduled. However, the related substances, 1,3-dimethylamylamine (DMAA), propylhexedrine and tuaminoheptane are in the Poisons Standard as follows:

#### **Schedule 10**

1,3-DIMETHYLAMYLAMINE (DMAA).

#### **Schedule 4**

PROPYLHEXEDRINE.

#### **Schedule 2**

TUAMINOHEPTANE.

### ***Scheduling history***

DMBA and DMHA have not been previously considered for scheduling; therefore a scheduling history is not available.

#### ***DMAA***

In August 2012, the ACMS considered a delegate-initiated proposal to list DMAA in Schedule 9 of the Poisons Standard, following New Zealand's temporary Class Drug Notice of 8 March 2012 advising that DMAA would be classified as a temporary class drug (equivalent to Schedule 9). New Zealand's temporary prohibition of DMAA came into effect on 9 April 2012.

Members noted that: there was inadequate evidence to suggest DMAA's toxicological and pharmacological properties warrant a Schedule 9 listing. DMAA is not listed in either Schedule IV to the *United Nations Convention on Narcotic Drugs, 1961* or in Schedule 1 to the *United Nations Convention on Psychotropic Substances, 1971*. There was a lack of supporting evidence to reach the conclusion that DMAA needs the same level of control as amphetamine. DMAA's toxicological properties meet the Appendix C (now Schedule 10) scheduling criteria. In the absence of a current



accepted therapeutic use, the stimulant effect that can induce a psychoactive effect, its active promotion as a party drug as well as a sports supplement, the lack of evidence of dependence, the significant number of adverse events including cardiac, nervous and psychiatric disorders that have been reported with use of DMAA including cerebral haemorrhage and heart attacks and the high potential for misuse and abuse, the committee recommended that the substance be placed in Appendix C (now Schedule 10). Based on DMAA's toxicity, lack of data supporting long-term safety, wide variability in potency of different doses of DMAA and the high risk of use, misuse and illicit use, the delegate placed DMAA in Schedule 10 effective on 8 August 2012<sup>7</sup>. [Reasons for the substance ban](#) were published on the TGA website.

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

#### **Schedule 10 – Proposed New Entry**

**1,3-DIMETHYLBUTYLAMINE (DMBA) AND OTHER ALIPHATIC ALKYLAMINES WITH STIMULANT PROPERTIES INCLUDING 1,5-DIMETHYLHEXYLAMINE (DMHA) *except* when separately specified in these schedules.**

#### **Index – Proposed New Entry**

**1,3-DIMETHYLBUTYLAMINE (DMBA) AND OTHER ALIPHATIC ALKYLAMINES WITH STIMULANT PROPERTIES INCLUDING 1,5-DIMETHYLHEXYLAMINE (DMHA)**

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisooheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA

#### **Schedule 10**

The applicant's reasons for the request are:

- 1,3-Dimethylbutylamine (DMBA) is a structural analogue of 1,3-Dimethylamylamine (DMAA) which was previously included in Schedule 10 of the Poisons Standard. It is proposed DMBA be added to the same schedule as DMAA due their structural and pharmacological similarity and potential for misuse and potential to result in harm. DMBA is a stimulant with no known therapeutic use.
- 1,3-Dimethylbutylamine (DMBA) has structural and likely pharmacological similarity with 1,3-Dimethylamylamine (DMAA). DMAA has been banned by regulatory agencies in United States of America (USA), United Kingdom, the Netherlands and Brazil because of its links to negative health events including as strokes, heart failure and sudden death. In 2012, Australia listed DMAA Appendix C (now Schedule 10). In New Zealand, DMAA was classified as a prescription medicine and it was noted that that it did not meet the definition of a dietary supplement. The applicant questions the classification of DMAA, given the deaths linked to DMAA internationally.
- DMBA is prohibited from sport under the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods, due to its structural similarity to DMAA under category 'S6. Stimulants'.
- DMBA appears to have become increasingly prevalent in supplements following the removal of DMAA from dietary supplements due to the intervention of food regulators in several countries. The effects of DMBA in humans have not been fully studied or clinically evaluated, and as such its efficacy and safety is unknown. Cohen, et al., (2014), called for regulatory agencies to act expeditiously to warn consumers and remove DMBA from supplements.

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<sup>7</sup> [Scheduling delegate's final decisions: DMAA, August 2012](#)



- A review of reports in online forums states that users had a strong stimulant effect. Anecdotal side effects reported by users of DMBA included 'jitteriness (sic), rapid heartbeat, dizziness, headache, and a crash after it has worn off'. There were also reports of depression and anxiety.
- Despite the lack of proof of the efficacy and safety of products containing DMBA they are readily available for purchase in Australian supplement stores and through online suppliers in Australia and overseas. Distributors are promoting products containing DMBA as supplement that improves athletic performance, increases weight loss and enhances brain function.
- Supplement products containing DMBA have promoted or implied that DMBA is a 'naturally occurring' botanical substance derived from Pouchong tea (*Camellia sinensis*). This claim has been proven to be false, an analysis of 25 authentic and commercial samples of *Camellia sinensis* tea leaves failed to detect DMBA.
- DMBA is prohibited from sport under the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods, due to its structural similarity to DMAA under category 'S6. Stimulants'.
- Since DMBA is a synthetically produced compound, the United States Food and Drug Administration (FDA) issued a warning in April 2015 that DMBA is not an approved dietary ingredient. The FDA determined products containing DMBA would not meet the definition of a "dietary supplement" and supplements containing DMBA are considered to be adulterated. The FDA has issued warnings, requiring manufacturers to immediately cease distribution and recover products containing DMBA already in the marketplace.
- Supplement manufacturers appear responsive to regulatory initiatives to restrict the supply of substances by converting to analogues or substances of similar effects. When regulatory agencies banned DMAA from all dietary supplements, alternative pressor amines such as DMBA appeared on the market replacing DMAA supplements. This demonstrates the need to regulate to prevent other compounds of this class from being added as ingredients to supplements.
- There are reports by supplement distributors online of plans to replace DMBA in supplements should DMBA be regulated in a similar way to DMAA. One of the suggested replacement substances is DMHA. Websites such as Herb Nutritionals and Mr Supplement have called DMHA a replacement for DMAA and DMBA. The websites also note that although there are unverified claims of the botanical nature of the compound, DMHA is likely to be synthetically produced.
- Given its structural similarity to DMAA, the application seeks to list DMBA on Schedule 10. Should this not be considered appropriate, the application seeks to list DMBA in Schedule 4.
- Given the evidence that more advanced analogues of DMBA, such as DMHA, and other aliphatic alkylamines with similar stimulant properties are reaching the market, the applicant also propose the scheduling apply to the class of substances. Scheduling of DMBA and its alkyl-analogues will protect public health from the potential adverse impacts of these unapproved substances. The adaptability of the supplements industry in developing chemically similar substances with similar stimulant like properties further underlines the need to be proactive and consider including an analogues clause that thereby schedules this class appropriately.

### ***Australian regulatory information***

DMBA and DMHA are not currently scheduled in Australia.

A search of the ARTG found no products containing DMBA or DMHA.

The Australian Sports Anti-Doping Authority (ASADA) has issued a warning to athletes, asserting that the presence of DMBA in a bodily sample collected during the competition period is an anti-doping rule violation and may attract a range of penalties including a 2-year ban from sport. If an anti-doping organisation can however demonstrate that the athlete intentionally took DMBA, the ban could be as high as 4 years.

## **International regulations**

### **1,3-Dimethylbutylamine (DMBA)**

DMBA is prohibited from sport under the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods, due to its structural similarity to DMAA under category 'S6. Stimulants'. WADA, noted that novel psychoactive substances (DMBA and DMHA) are derived from stimulants and marketed for these effects. The substances arrive on the market with little pharmacological data and the use of non-approved drugs in humans poses risks for health. Under the World Anti-Doping Code, use of these substances by athletes may result in ineligibility to compete in sport for up to 4 years. WADA confirmed DMBA is deemed to be a health risk given it is a non-approved drug with little pharmacological data regarding its effect on humans.

The US FDA issued a statement in relation to the inclusion of DMBA in dietary supplements<sup>8</sup> following warning letters to 14 companies sent in April 2015, where DMBA was considered an adulterant in 17 products. The US FDA considers any dietary supplement containing DMBA to be "adulterated".

In New Zealand, DMBA is classified as a psychoactive substance and its sale and supply are prohibited under the Psychoactive Substances Act. Information on The NZ Office of the Psychoactive Substances Regulatory Authority website<sup>9</sup> states:

*"DMBA has only recently emerged as an active ingredient in dietary supplements worldwide and much of what is deduced about the activity of DMBA is based on its structural similarity to DMAA. Preliminary studies show that, as its structure suggests, DMBA has pressor effects (raises blood pressure), similar to, but less potent than those exhibited by DMAA, thereby supporting the position that DMAA and DMBA are functionally similar. DMBA is considered to be capable of producing a psychoactive effect when consumed by humans on the basis that DMAA is a psychoactive substance and DMBA is structurally and functionally similar to DMAA.*

*Products containing DMBA generally appear to be positioned as dietary supplements or supplemented foods and are intended as pre-workout supplements. None of the products concerned to date meet the definition of a dietary supplement because the ingredients are clearly not intended to supplement the amount normally derived from food. The products also cannot be sold as supplemented foods because supplemented foods are prohibited from containing intoxicating substances (i.e., psychoactive substances).*

*On the basis that DMBA is considered to be capable of producing a psychoactive effect when consumed and that the products concerned cannot be sold as dietary supplements or supplemented foods, pre-workout supplements containing DMBA are considered to be unapproved psychoactive products."*

### **1,5-Dimethylhexylamine (DMHA)**

No information could be found regarding the status of DMHA in the USA. However, the US FDA website includes warnings regarding DMAA, DMBA and BMPEA ( $\beta$ -methylphenylethylamine, reportedly sourced from *Acacia rigidula*) in Dietary Supplements<sup>10</sup>. None of these substances have been determined to meet the statutory definition of a dietary ingredient. The US FDA issued warning letters to 5 companies sent in April 2015 regarding BMPEA and *Acacia rigidula*.<sup>11</sup>

No information could be found regarding the status of DMHA in New Zealand.

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<sup>8</sup> [DMBA in Dietary Supplements](#)

<sup>9</sup> [DMBA in Dietary Supplements](#)

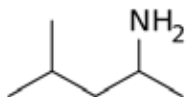
<sup>10</sup> [BMPEA in Dietary Supplements](#)

<sup>11</sup> [Cosmetic Ingredient Hotlist](#)

In Canada, DMHA is known as 'octodrine and its salts' and is listed as prohibited on the Health Canada Cosmetic Ingredient list.<sup>12</sup>

### Substance summary

#### 1,3-Dimethylbutylamine (DMBA)



**Figure 1.2A: Structure of DMBA**

DMBA, is an aliphatic amine stimulant that is structurally related to DMAA, where a butyl group replaces the amyl group. DMBA is commonly found in OTC supplements commonly described as 'pre-workouts' and 'fat burners'. DMBA has a molecular weight 101.2, and molecular formula C<sub>6</sub>H<sub>15</sub>N.

Some products market DMBA on labels as a compound extracted from Pouchong tea and infer that it is a natural product, rather than synthetic. This may imply safety for consumption. A similar marketing approach was used for DMAA as a geranium extract. However, Cohen, *et al.*, (2014) noted 'we are unaware of any scientific evidence that DMBA has ever been extracted from any plant, while synthetic DMBA is easy to synthesise and widely available'.

DMBA belongs to the family of pressor-amines including DMAA, tuamine and propylhexedrine. The concentrations found in the supplements analysed strongly suggest DMBA is synthetically mass-produced to create pharmaceutical effects.

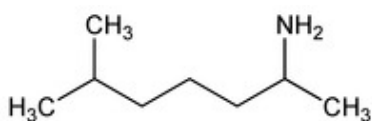
DMAA was listed in Schedule 10 in 2012. The use of DMBA and structurally related stimulants has generated concern in medical circles due to their amphetamine-like effect and possible health consequences. It appears manufacturers are intentionally including DMBA in sports supplements to restore, and possibly surpass, the effect generated by DMAA before its prohibition.

In the scheduling of DMAA in August 2012 the ACMS noted:

- there are risks due to DMAA's toxicity
- DMAA has no current accepted therapeutic use
- DMAA has a stimulant effect which can induce a psychoactive effect
- there are a number of significant adverse events including cardiac, nervous and psychiatric disorders that have been reported with use of DMAA including cerebral haemorrhage (stroke) and heart attacks
- there is a wide variability in the potency of the different doses of DMAA

As DMBA is a new ingredient there do not appear to be any peer-reviewed studies assessing the pharmacology, toxicology, and safety of the compound.

#### 1,5-Dimethylhexylamine (DMHA)



**Figure 1.2B: Structure of DMHA**

<sup>12</sup> [Is this the new DMAA?](#) and [The New DMAA \(DMHA / 2-Aminoisoheptane / Octodrine\)](#)

DMHA, also referred to as Octodrine, 6-methyl-2-heptanamine, molecular weight 129.3, has the following molecular formula  $C_8H_{19}N$ . DMHA is an  $\alpha$ -adrenergic agonist and decongestant. The hydrochloride salt is crystalline and soluble in water, and the Merck Index reports LD50 in mice, rats (mg/kg): 59, 41.5 i.p. Websites report that DMHA is found in sufficient doses in nature, in particular in the *Kigelia africana* fruit and state that this allows it to be considered a dietary supplement and get approval from the relevant authorities<sup>13</sup>. Website product names that contain DMHA include *Giant Sports Giant Rush*.

There has been limited research regarding the harms and possible therapeutic benefits associated with the use of the substances proposed for scheduling. The potential side effects of this class of stimulants are wide ranging. Significant adverse events include cardiac, nervous and psychiatric disorders that have been reported with use of DMAA. As an analogue of this Schedule 10 substance, DMBA is believed to pose similar health risks.

The health risks from DMBA in pharmacological doses are unknown. DMBA has never been studied in humans. DMBA has pressor effects and DMBA should be considered an active pharmaceutical ingredient that requires rigorous clinical testing and evaluation prior to marketing.

These substances are being used by athletes and the broader community as a stimulant before physical activity. Supplements containing DMBA have been marketed to improve athletic performance, increase weight loss and enhance brain function.

Available information on pre-workouts and thermogenics suggest that this part of the supplement industry is expanding considerably in Australia.

DMBA can be included in sports supplements as part of a proprietary blend and as such product labelling usually does not specify the exact dosage per serving

The study conducted by Cohen et al (2015) tested the relative concentrations of DMBA in a range of sports supplements sold in the USA ranging from 13 mg to 120 mg per serving. Based on the maximum daily number of servings some products allowed for a daily intake of up to 320 mg. As there has been no testing on the safety or efficacy of this compound it is unknown what level of intake (if any) would be safe. Australian supplement websites and internet forums report taking three to five times the recommended daily dose in one serving in order to experience the full psychoactive effect.

An analysis of numerous supplements on the Australian market produced data showed two products from the pre-workout and weight management category contained DMBA and DMAA at high concentrations and other products with low-level cross-contamination in complex botanical ingredients.

Due to the purported psychoactive properties of DMBA, it is used primarily as a stimulant to increase focus during workouts. It also has the potential to be used for other purposes and has been promoted as a study aid as its stimulant properties are reported to increase mental focus.

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACMS advice to the delegate***

The committee advised that a new entry be created for 1,3-dimethylbutylamine (DMBA) and other alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10, **except** when separately specified in these schedules, as follows:

#### **Schedule 10 – New Entries**

**1,3-DIMETHYLBUTYLAMINE (DMBA) except when separately specified in these schedules.**

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<sup>13</sup> [The new DMAA \(DMHA / 2-Aminoisoheptane / Octodrine\)](#)

1,5-DIMETHYLHEXYLAMINE (DMHA) **except** when separately specified in these schedules.

ALKYLAMINES WITH STIMULANT PROPERTIES **except** when separately specified in these schedules.

### **Index – New Entries**

#### **1,3-DIMETHYLBUTYLAMINE (DMBA)**

cross reference: DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

#### **1,5-DIMETHYLHEXYLAMINE (DMHA)**

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

#### **ALKYLAMINES WITH STIMULANT PROPERTIES**

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate)

Schedule 10

The committee also recommended an implementation date of **1 October 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

The reasons for the advice comprised the following:

- There is a significant health risk.
- DMBA is readily available in Australia despite lack of proof of efficacy and safety, and there is no current accepted therapeutic use.
- DMBA is listed by ASADA and WADA in anti-doping rules. WADA considers DMBA to be a health risk due to little pharmacological data of its effects in humans and is a non-approved drug.
- The potential for misuse and abuse is high.

#### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS advice
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to create new entries for 1,3-dimethylbutylamine (DMBA) and other alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10, except when separately specified in these schedules. The proposed Schedule entry is as follows:

#### **Schedule 10 – New Entries**

1,3-DIMETHYLBUTYLAMINE (DMBA) **except** when separately specified in these schedules.

1,5-DIMETHYLHEXYLAMINE (DMHA) **except** when separately specified in these schedules.

ALKYLAMINES WITH STIMULANT PROPERTIES **except** when separately specified in these schedules.

#### **Index – New Entries**

##### **1,3-DIMETHYLBUTYLAMINE (DMBA)**

cross reference: octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

##### **1,5-DIMETHYLHEXYLAMINE (DMHA)**

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

##### **ALKYLAMINES WITH STIMULANT PROPERTIES**

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate)

Schedule 10

The proposed implementation date is **1 October 2017**, since this is the earliest possible implementation date.

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 a substance; (b) the purposes for which a substance is to be used 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 of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- There is a significant health risk.
- DMBA is a structural analogue of DMAA, which was previously included in Schedule 10 of the Poisons Standard. DMBA is readily available in Australia, despite lack of proof of efficacy and safety, and there is no current accepted therapeutic use.
- DMBA is listed by ASADA and WADA in anti-doping rules. WADA considers DMBA to be a health risk due to little pharmacological data of its effects in humans and is a non-approved drug.
- The potential for misuse and abuse is high.

### ***Public submissions on the interim decision***

No public submissions were received in response to the interim decision for 1,3-dimethylbutylamine (DMBA) and other aliphatic alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA).

### ***Delegate's final decision***

As no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to create new entries for 1,3-dimethylbutylamine (DMBA) and other alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10. The implementation date is **1 October 2017**.

## **1.3. Ulipristal**

### ***Referred scheduling proposal***

An application was submitted to amend the Schedule 3 entry for ulipristal by including 'ulipristal for emergency post-coital contraception' in Appendix H.

### ***Current scheduling status and relevant scheduling history***

Ulipristal is currently listed in Schedules 3 and 4 of the Poisons Standard.

#### **Schedule 4**

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

#### **Schedule 3**

ULIPRISTAL for emergency post-coital contraception.

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

#### **Appendix H – Proposed New Entry**

ULIPRISTAL for emergency post-coital contraception

#### **Index – Proposed Amendment**

ULIPRISTAL

Schedule 4

Schedule 3

Appendix H

The applicant's reasons for the request are:

- Emergency contraception (EC) gives women a simple, safe and convenient option to avoid an unintended pregnancy if used within a few days of UPSI. However, while sales of EC in Australia are approaching 650,000 units per year (IMS October 2015 – September 2016), knowledge about the availability and use of EC remains low.
- The applicant refers to a 2011 study surveying 632 Australian women aged 16 – 35 that concluded that although Australian women have a high level of awareness of EC, their inadequate knowledge limits its potential to assist in reducing unintended pregnancy and abortion rates: "A media



campaign could be an effective means of disseminating information about the pharmacy availability, time frame for effective use and safety of EC”.

- The applicant refers to a 2008 study surveying 627 Australian university students regarding knowledge and attitudes about emergency contraception and their understanding of the risk for pregnancy that concluded that “EC needs to be better understood by all members of the community as a back-up contraceptive method after unprotected sexual intercourse to reduce the number of terminations of pregnancy after unprotected sexual intercourse to reduce the number of terminations of pregnancy and unwanted pregnancies” and “Allowing EC to be advertised via the mass media has the greatest potential to improve general community knowledge about EC”.
- The applicant also refers to US and UK European studies that found media campaigns increased community awareness and education about this method of contraception and increased contact with EC hotlines and did not invoke any special controversy.
- The applicant estimates approximately 200 000 unplanned pregnancies and 80 000 terminations in Australia a year in 2005. Two thirds of women presenting for abortions in Australia reported contraception use at time of conception. The applicant’s data shows the number of abortions decreased slightly since EC became available, but its availability has not had a significant impact.
- The applicant states that under the TG Act, ‘Unless a substance is included in Appendix H, members of the community cannot be given any product-specific information including via company websites, display material in pharmacies or even via training material for pharmacy assistants.’
- The applicant proposes to determine the media used by women of reproductive age to obtain information on contraception options, including EC and identify the sources of information for the different age groups and how women in each age group prefer to receive this information. This will be used to develop appropriate, targeted and responsible direct-to-consumer advertising and informational material specific to ulipristal that supports and complements the role of pharmacists in assisting women facing the possibility of unintended pregnancy. This could include a dedicated web site, consumer leaflets for distribution through pharmacies, doctors’ surgeries, family planning centres etc. and social media as well as the more traditional print and broadcast media.
- The applicant proposes involving professional pharmacy bodies in campaigns to educate women on the use of EC in general and ulipristal in particular with the aim of reducing the number of unwanted pregnancies and abortions (with education and training material covering the condition, the role and benefit of the product as EC, pharmacist involvement). The applicant requests a 12 month delay for implementation from the Schedule 3 implementation date to allow pharmacists to become familiar with the use of ulipristal as Schedule 3.
- Ulipristal is advertised in 25 EU countries. Branded advertising is allowed in 13 of those countries with ‘category’ (emergency contraception) advertising in the other 12 countries.
- Consumer surveys have shown that knowledge of the availability, safety and effects of EC is poor among Australian women and that this may act as a barrier to its use (Hobbs 2011, Calabretto 2008). Specific, targeted, responsible advertising that reinforces the important role of pharmacists has considerable potential to reverse this situation with a significant reduction in unwanted pregnancies and consequent abortions. This would have important direct and indirect benefits for public health and in avoiding the social and economic costs of abortions.
- The advertising of ulipristal is unlikely to lead to inappropriate patterns of medication use: as pharmacists are involved in every sale, the pack contains a single tablet to be taken as soon as possible after UPSI, so potential for inappropriate or incorrect use is low and all forms of advertising will emphasize the important role of pharmacists in advising women on the correct and appropriate use of ulipristal.
- The sponsor for ulipristal will lodge an application to change the label to the TGA to amend the label for the existing ulipristal acetate 30 mg tablet blister pack to match the requirements for



schedule 3 medicines (adding a 'pharmacist only medicine' signal heading plus indications & directions for use) and in line with this proposes to comply with advertising of therapeutic goods in Australia must comply with the Therapeutic Goods Advertising Code (TGAC). Section 6(3)(e) of the Code requires the inclusion of words to the effect of: "YOUR PHARMACIST'S ADVICE IS REQUIRED" in all advertisements for schedule 3 medicines. This message will be a key feature in all advertising material.

- Pharmacists remain involved in sale of Schedule 3 medicines and the CMI will reflect the involvement of pharmacists in counselling consumers.
- Experience with the non-prescription use of levonorgestrel EC since 2003 provides reassuring evidence that pharmacy access has not created any particular indirect risk. Studies that have examined the use of EC when provided directly at the pharmacy or given in advance of need, have shown that, compared to prescription provision, direct access:
  - Does not increase sexual risk taking behaviour in adolescents (Ekstrand 2008, Harper 2008, Raine 2012).
  - Does not lead to increased frequency of unprotected intercourse (Marston 2005, Moreau 2006).
  - Does not lead to decreased use of effective methods of contraception (Marston 2005, Raine 2005, Ziebland 2005, Moreau 2006, Ekstrand 2008, Moreau 2008) and women's EC experience is actually described as a motivating factor leading to more consistent use of regular contraception (Gainer 2003).
  - Does not lead to increased rates of sexually transmitted infections (Raymond 2006, Raine 2005).
- The applicant states that ulipristal does not have an abortifacient action.
- The applicant proposes to work with pharmacy organisations to provide pharmacists educational materials in relation to ulipristal to meet legal and professional obligations and supports them in that role.
- The applicant proposes to discuss parameters for advertising with pharmacy organisations to ensure advertising and educational material will be framed to increase awareness of the availability of EC through pharmacists and to complement the pharmacist's role in ensuring the 'quality use' of ulipristal.
- While nearly 70 per cent of Australian women of reproductive age are using some form of contraception (Richters 2003), the uptake of the most effective forms of contraception, long-acting reversible contraception, remains low (Garrett 2015), leaving many women at an increased risk of an unplanned pregnancy.
- Women have expressed that the availability of emergency contraceptive pills over the counter is advantageous because it gives them more control over their contraception (Hobbs 2009).
- The need for more information about fertility and contraception, particularly emergency contraception, has been highlighted by both women and healthcare professionals across a number of studies. Young women have expressed the need for more information and education about emergency contraception, as there is little information available to them (Hobbs 2009). Not only is there a need for more information, but both women and healthcare professionals have expressed the need for more inclusive and easier to access contraceptive information, including easy-to-understand wording, and information in audio and video formats (Garrett 2015).
- Women may be receiving conflicting, out-dated, inaccurate and anecdotal information, rather than evidence-based, current information.
- Women have reported frustration that healthcare providers had not informed them of alternatives to the contraceptive pill and many felt that they were unable to make informed choices about

contraception because of limited understanding of their available options and how they work (Garrett 2015).

- Poor knowledge about emergency contraception has been linked to its non-use.
- When women take responsibility for their healthcare and seek EC from a pharmacy, they report being concerned about a lack of privacy within the pharmacy, resulting in feelings of awkwardness and embarrassment (Hobbs 2011). These women reported that they want the pharmacists' role to be limited and their experience at the pharmacy to be as short as possible (Hobbs 2009).
- Consumers want to exercise more control in the management of their own health, particularly in this personal and sensitive areas. Responsible, targeted advertising could start to address this issue while increasing community knowledge of the availability of this simple, safe and effective option for preventing unwanted pregnancy and at the same time supporting and enhancing the role of pharmacists in helping women through this difficult time
- Ulipristal is a safe and effective medicine for the prevention of unwanted pregnancy
- The ability to advertise ulipristal and make educational information available to consumers will significantly improve public awareness and knowledge of this simple, safe, effective and convenient option for Australian women to prevent unwanted pregnancies. This increased awareness has the potential to significantly reduce the number of abortions with consequent benefits for public health.

### ***Australian regulatory information***

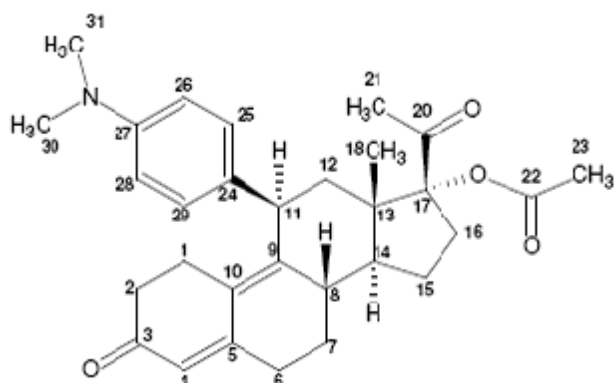
Ulipristal acetate was included in the ARTG on 6 March 2015.

### ***International regulations***

Ulipristal was first approved in the EU in May 2009, where it is not subject to medical prescription and has marketing authorisation with the requirement of periodic safety update reports.

Ulipristal is approved as prescription emergency contraception in New Zealand, Canada and the USA. Ella was approved in the USA in August 2010. In Canada, ulipristal is marketed by two companies, Labratoire HRA Pharma as Ella in 30 mg tablet form and Allergan Pharma Co as Fibrystal in 5 mg tablet form.

### ***Substance summary***



**Figure 1.3: Structure of ulipristal acetate**

Ulipristal acetate (chemical name: 17 $\alpha$ -acetoxy-11 $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione) is an orally-active synthetic selective progesterone receptor modulator that acts via high affinity binding to the human progesterone receptor. When used for emergency contraception the

mechanism of action is inhibition or delay of ovulation via suppression of the luteinizing hormone surge.

Ulipristal is indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

### ***Pre-meeting public submissions***

Fourteen (14) submissions were received.

*Thirteen (13) submissions supported the scheduling proposal. Main points were:*

- Ulipristal acetate provides increased efficacy and a longer window of opportunity to prevent unwanted pregnancy compared to other available emergency contraception.
- An increased uptake of emergency contraception has the potential to prevent unplanned pregnancies, contributing to the reduction of direct and indirect costs to the health care system.
- There would be a direct reproductive health benefit for women by enabling them to avoid unplanned pregnancies.
- Some women have misconceptions about its use, especially the time period of its effective use. It is also not widely understood by pharmacists and other practitioners.
- The likelihood of “inappropriate use” would be minimised with comprehensive training with the pharmacy sector and education with women.
- EC is extremely safe, even when used repeatedly. Compared with the potential health risks of pregnancy, taking ECPs to prevent unintended pregnancy is much safer.
- The pack contains a single tablet so the potential for inappropriate or incorrect use is very low.
- Ulipristal will remain in Schedule 3 meaning a pharmacist must be personally involved in every sale.
- There should also be an expansion of the list of health professionals to include remote area nurses, midwives and nurse practitioners to supply the ulipristal acetate to women in remote and isolated areas.
- Direct to consumer marketing will not only promote UPA, but importantly it will also serve to raise awareness of emergency contraception more generally in the community.
- All forms of advertising will emphasise the important role of pharmacists in advising women on the correct and appropriate use.
- A UK advertising campaign on emergency ulipristal was shown to be worthwhile.

*Two (2) submissions did not support the scheduling proposal. Main points were:*

- There may be an increase in requests for the medicine from third parties with advertising.
- An Appendix H listing would not be in the public interest.
- Short period of experience as Schedule 3 medicine.

The [public submissions](#) will be made available on the TGA website.

### ***Summary of ACMS advice to the delegate***

The committee advised that the Schedule 3 entry for ulipristal be amended by including ‘ulipristal for emergency post-coital contraception’ in Appendix H, as follows:

### **Schedule 3**

ULIPRISTAL for emergency post-coital contraception.

### **Appendix H – New Entry**

ULIPRISTAL for emergency post-coital contraception

### **Index – Amend Entry**

### **ULIPRISTAL**

Schedule 4

Schedule 3

Appendix H

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- Public health is likely to be improved, since increased community knowledge may improve access to this product, which will likely reduce the incidence of unplanned pregnancies.
- Low toxicity and low potential for abuse, since only available as single dose tablet.
- Risk of misuse may be mitigated through need for pharmacist counselling and supply. Ulipristal is not an abortifacient therefore risk of ‘abuse’ is minimal.
- Listing in Appendix H is supported by the majority of clinical stakeholders. Concerns raised by pharmacists may be mitigated through a delayed start date.
- A delayed start date will give some lead time for pharmacists to gain experience with the relatively new Schedule 3 listing.

### ***Delegate’s considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate’s interim decision***

The delegate’s interim decision is to amend the Schedule 3 entry for ulipristal by including ‘ulipristal for emergency post-coital contraception’ in Appendix H. The proposed Schedule entry is as follows:

### **Schedule 3**

ULIPRISTAL for emergency post-coital contraception.

## Appendix H – New Entry

ULIPRISTAL for emergency post-coital contraception

### Index – Amend Entry

#### ULIPRISTAL

Schedule 4

Schedule 3

Appendix H

The proposed implementation date is **1 February 2018** to allow sufficient time for experience to be gained with the relatively new Schedule 3 listing prior to advertising.

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 a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Public health is likely to be improved, since increased community knowledge may improve access to this product, which will likely reduce the incidence of unplanned pregnancies.
- Low toxicity and low potential for abuse, since only available as single dose tablet.
- Risk of misuse may be mitigated through need for pharmacist counselling and supply. Ulipristal is not an abortifacient therefore risk of 'abuse' is minimal.
- Listing in Appendix H is supported by the majority of clinical stakeholders. Concerns raised by pharmacists may be mitigated through a delayed start date.
- A delayed start date will give some lead time for pharmacists to gain experience with the relatively new Schedule 3 listing.

#### ***Public submissions on the interim decision***

No public submissions were received in response to the interim decision for ulipristal.

#### ***Delegate's final decision***

As no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to amend the Schedule 3 entry for ulipristal by including 'ulipristal for emergency post-coital contraception' in Appendix H. The implementation date is **1 February 2018**.

## 1.4. Ibuprofen

### ***Referred scheduling proposal***

An application was submitted with the following proposal to amend the Schedule 3 entry for ibuprofen to include a modified release dosage form of 600 mg of ibuprofen per dosage unit in packs of 32 or less dosage units when labelled:

- a) with a recommended daily dose of 1200 mg or less of ibuprofen; and

- b) not for the treatment of children under 12 years of age;

and include in Appendix H ibuprofen 600 mg in modified release dosage form.

### ***Current scheduling status***

In monotherapy preparations, ibuprofen is included in Schedules 4, 3 and 2 as follows:

#### **Schedule 4**

IBUPROFEN **except**:

- a) when included in or expressly excluded from Schedule 2 or 3; or
- b) in preparations for dermal use.

#### **Schedule 3**

IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled:

- a) with a recommended daily dose of 1200 mg or less of ibuprofen; and
- b) not for the treatment of children under 12 years of age;

**except** when included in or expressly excluded from Schedule 2.

#### **Schedule 2**

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

- a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or
- b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:
  - i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent);
  - ii) packed in blister or strip packaging or in a container with a child-resistant closure;
  - iii) in a primary pack containing not more than 25 dosage units;
  - iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels;
  - v) not labelled for the treatment of children 6 years of age or less; and
  - vi) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

It is also included in **Appendix F, Part 3** under the entry:

IBUPROFEN:

**101:** Don't use [*this product/name of the product*]:

If you have a stomach ulcer

In the last 3 months of pregnancy [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.*]

If you are allergic to (name of substance) or anti-inflammatory medicines

**104:** Unless a doctor has told you to, don't use [*this product/name of the product*]:

For more than a few days at a time

With other medicines containing (name of substance) or other anti-inflammatory medicines

If you have asthma

If you are pregnant [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.*]

- Ibuprofen is listed in Schedule 4 when in compounded products with paracetamol, in a primary pack containing more than 30 dosage units.
- Ibuprofen is listed in Schedule 3 when in compounded products with paracetamol in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.
- Ibuprofen is also listed in Schedule 2 when compounded in products with paracetamol in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack.

### ***Scheduling history***

In November 1985, the National Health and Medical Research Council (NHMRC) considered a request to change to Schedule 2 (currently in Schedule 4 of UPS) as Ibuprofen was not scheduled in Victoria. It was agreed there were anaphylactic problems with people sensitive to aspirin. It was decided not to alter the scheduling.

In November 1987 the NHMRC considered a request to move ibuprofen from Schedule 4 to Schedule 2 with pack size restrictions. The committee was of the opinion that there was a place for ibuprofen outside Schedule 4. Recommendation for a new Schedule 3 entry with pack size restrictions of less than 50 tablets or capsules (200 mg).

In May 1995, the NDPSC considered proposal for a new Schedule 2 entry for ibuprofen and agreed to a new entry. Schedule 4 entry amended. New Schedule 2 for ibuprofen in divided preparations for oral use containing 200mg or less with a recommended dose of 1200mg or less.

In November 1998, the NDPSC considered an application for ibuprofen liquid suspension 100 mg/5 mL to be rescheduled from Schedule 4 to Schedule 2. Overall, the committee considered that a Schedule 3 classification was more appropriate for this formulation, and agreed that the Poisons Standard be amended accordingly. The committee agreed that a maximum daily dose should be stipulated, but because the proposed pack size was 200 mL (maximum of 4 g ibuprofen) a restriction on total content was not required for this classification. A new entry for Schedule 3 was agreed in undivided preparations for oral use when labelled with a recommended daily dose of not more than 1200 mg of ibuprofen.

In May 2000, the NDPSC considered a proposal to amend the Schedule 2 entry for ibuprofen to include oral liquid preparations containing more than 20 mg/1 mL. The committee considered the safety profile of ibuprofen and that Schedule 2 is appropriate when used in analgesic dose for minor and temporary ailments for short periods. The committee was seeking consistency with divided dose formulations.

In June 2003, the NDPSC considered a proposal to exempt ibuprofen from scheduling in divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 24 or less dosage units when labelled with a maximum recommended daily dose of 1200 mg of ibuprofen. The NDPSC decided to exempt ibuprofen from scheduling as requested, but with an amended maximum pack size (25 dosage units) and additional restrictions as follows: ibuprofen as the only therapeutically active constituent other than an effervescent agent; and requirements for label warnings (consistent

with Appendix F warnings for Schedule 2 ibuprofen). The minutes note that the NDPSC had agreed that the schedule wording should be comparable with that of the current aspirin and paracetamol entries.

In October 2003, following consideration of further public submissions, the NDPSC made some amendments to the label warning statements required for ibuprofen when exempted from scheduling, in particular, by adding warnings not to use the product unless advised by a doctor in children ages 6 years or less, or by people aged 65 years or over.

The NDPSC subsequently made some editorial amendments to the Schedule 2 exemption in June 2004 and February 2005.

In August 2010 the NDPSC considered the scheduling of paracetamol in combination with ibuprofen in June 2010. At that time, divided dose combinations containing up to 200 mg ibuprofen + 500 mg paracetamol were included in Schedule 2 (when labelled with a maximum daily dose of 1200 mg ibuprofen, and in packs of up to 100 dosage units). The NDPSC recommended, and the delegate confirmed, that the scheduling of ibuprofen and paracetamol that was current at that time remained appropriate.

In June 2011 the ACMS considered a proposal from the Advisory Committee on Non-prescription Medicines (ACNM) that the delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination.

The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The delegate agreed with the ACMS advice.

In February 2013 the ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less, and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The delegate agreed with the ACMS advice.

In June 2012, the ACMS considered a submission to reschedule ibuprofen from Schedule 2 to unscheduled when in divided preparations containing 200 mg or less of ibuprofen in fixed dose combination with 5 mg or less of phenylephrine, in packs containing not more than 25 tablets. ACMS advised the delegate that ibuprofen in combination with phenylephrine should be exempt from scheduling, as requested. The delegate decided to also restrict the scheduling exemption to use for the treatment of adults and children aged 12 years of age and over.

In November 2015, the ACMS considered a submission to amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less. The ACMS advised that paracetamol should be included in Schedule 2 when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a pack of not more than 3 day supply. The delegate agreed with the ACMS and made an interim decision based on the ACMS advice. After deferring their final decision to



give consideration to a late submission received during the interim decision consultation period, the delegate decided to vary their decision. In view of the dosage levels of paracetamol and ibuprofen the delegate considers it is more appropriate to limit the Schedule 2 part a) entry to 12 dosage units per pack rather than 3 days' supply packs as this would ensure the total paracetamol available in the pack would not be excessive.

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

#### **Schedule 3 – Proposed Amendment**

IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled:

- a) with a recommended daily dose of 1200 mg or less of ibuprofen; and
- b) not for the treatment of children under 12 years of age;

IBUPROFEN in a modified release dosage form containing 600 mg of ibuprofen per dosage unit in packs of 32 or less dosage units when labelled:

- a) with recommended daily dose of 1200 mg or less; and
- b) not for the treatment of children under 12 years of age.

**except** when included in or expressly excluded from Schedule 2.

#### **Appendix H – Proposed New Entry**

##### **Ibuprofen 600 mg in a modified release dosage form**

The applicant's reasons for the request are:

- The total daily dose of ibuprofen 600 mg IR/ER does not exceed 1200 mg and is therefore identical with that already approved for non-prescription ibuprofen 200 mg and 400 mg IR products.
- Ibuprofen 600 mg IR/ER is bioequivalent to ibuprofen 200 mg IR tablets after single and multiple doses in terms of AUCL, AUCI, AUC0-12h, and overall Cmax.
- The human safety profile for ibuprofen 600 mg IR/ER tablet is favourable and similar to that observed for ibuprofen 200 mg IR.
- The new formulation approximates the immediate release characteristics of an ibuprofen 200 mg tablet, combined with extended release properties to maintain plasma concentrations adequate to provide up to 12 hours of pain relief with less frequent dosing.
- Ibuprofen 600 mg IR/ER is efficacious for up to 12 hours in a model of dental pain, and this efficacy is sustained over multiple doses.
- The non-prescription availability of ibuprofen 600 mg IR/ER as Schedule 3 provides an alternative option not only to the limited range of non-prescription modified release analgesics available in the market for short-term use but also to existing immediate release analgesic products that fall short of providing longer lasting relief from persistent pain conditions likely to last for more than 6 hours.
- Creating a Schedule 3 and Appendix H entry of ibuprofen 600 mg IR/ER is consistent with the current scheduling status of comparable non-prescription analgesics namely, naproxen 600 mg modified release, diclofenac 25 mg immediate release and paracetamol 665 mg sustained release

that are permitted to be advertised as a result of inclusion in Appendix H or in the case of paracetamol, inclusion in Schedule 2.

- Ibuprofen 400 mg IR is currently included in Schedule 3, however, the information in this application is specific and relevant only to ibuprofen 600 mg IR/ER and does not translate to ibuprofen 400 mg IR. Hence, the proposal to include ibuprofen in Appendix H with specific conditions by stipulating the dosage strength and form, i.e. ibuprofen 600 mg in a modified release dosage form. This approach is consistent with the dimenhydrinate inclusion in Appendix H, which has specific conditions applied stipulating the indication of use that the product can only be advertised for.
- The non-prescription availability and advertising of ibuprofen 600 mg IR/ER as a Schedule 3 medicine provides significant benefits are listed below:
  - The non-prescription approval of ibuprofen 600 mg IR/ER would provide an alternative option to a limited range of modified release analgesics available in the market for short term use and existing immediate release analgesics that fall short of providing sustained effect for longer lasting (more than 6 hours) pain conditions.
  - Improved access to a treatment option that provides rapid and extended analgesic relief over 12 hours reducing the frequency of dosing for those consumers who cannot optimally manage their persistent pain lasting for more than 6 hours with existing immediate release analgesics.
  - Breakthrough pain that can occur with short-acting analgesics in addition to the need to wake during the night to take a medication can be avoided with the use of ibuprofen 600 mg IR/ER.
  - Quality Use of Medicines principles will be supported by advertising and consumer programmes which are effective communication tools to educate consumers on this new dosage form, drive familiarity of appropriate use and encourage consumers to consult a pharmacist.
  - Consultation with a pharmacist will ensure appropriate and quality use of the product and improved clinical outcomes for consumers including those currently accessing analgesics for self-selection from grocery and pharmacy channels who may not be optimally managing their pain condition.
  - Cost savings associated with the use of ibuprofen 600 mg IR/ER over immediate release formulations and economic benefits resulting from self-care and use of professional pharmacy resources.
- Suggested measures to manage potential risks associated with Schedule 3 entry and advertising ibuprofen 600 mg IR/ER (i.e. misuse, overdose, accidental ingestion, drug interactions, delay in treatment of an underlying condition, prolonged use) include:
  - Mandatory requirement for pharmacist intervention at the point of sale ensures that only consumers who have pain lasting for more than 6 hours have access to and use ibuprofen 600 mg IR/ER for the shortest period of time and inappropriate use for transient pain does not occur.
  - Consumer labelling contains necessary information to ensure correct and safe use of the medicine. The front/ main panel includes dosing-related statements, an entirely unique feature that differentiates the product from other non-prescription analgesics to emphasise correct dosing ensuring safe use of the product).
  - Implementation of education programs, resources and promotional materials (facilitated by inclusion in Appendix H) to educate consumers on the difference between persistent and transient pain ensuring appropriate and quality use of ibuprofen 600 mg IR/ER.

- Education programs for pharmacists to supplement current resources to help increase their awareness of a new dosage form of ibuprofen and ensure that request for the product by consumers is managed appropriately.

### ***Australian regulatory information***

A search of the ARTG<sup>14</sup> returned 240 entries for ibuprofen containing products. The ibuprofen products are approved for treatment of infants to adults and come in multiple dosage strengths and forms. Dosage strength and forms include 200 mg and 400 mg capsules, gel capsule, liquid capsule, 200 mg and 400 mg tablets and film coated tablets, 20 mg/1 ml, 40 mg/1 ml, 100 mg/5 ml oral liquids, 200 mg and 400 mg effervescent granules, 100 mg chewable tablets.

In addition to the oral forms there are 50 mg/g topical gels and 400 mg and 800 mg vials for injection.

Combination products include ibuprofen with codeine, ibuprofen with paracetamol and ibuprofen with pseudoephedrine. The ARTG also included entries for ibuprofen lysine 324 mg tablets and capsules as well as ibuprofen sodium dihydrate 256 mg capsule and tablet.

A search of the Database for Adverse Events Notifications (DAEN) between January 1985 and August 2016 resulted in 1229 cases related to ibuprofen with 819 cases with a single suspected medicine. Of these 36 cases were reported to have resulted in death.<sup>15</sup>

### ***International regulations***

There is no modified-release OTC ibuprofen product in New Zealand. Medsafe<sup>16</sup> regulates ibuprofen up to 200 mg for external use and oral use with pack size restrictions for general sale and/or pharmacy only depending on dose unit number or total ibuprofen amount. Up to 400 mg in single dose form in packs of less than 50 dose units are restricted without consent of the Minister or the Director-General. Dosages over 400 mg are considered prescription medicines. An 800 mg ibuprofen sustained release tablet is prescription-only in New Zealand.

In February 2016, Health Canada<sup>17</sup> switched a modified release oral dosage form that provides 600 mg or less per dosage unit of ibuprofen to non-prescription status. This is available as 'Advil 12 Hour', containing 'ibuprofen extended release tablets BP, 600 mg'. This appears to be the formulation proposed in the current scheduling request.<sup>18</sup>

February 2016: Health Canada updated its Summary Safety Review of prescription ibuprofen to investigate the link between ibuprofen at high doses and serious heart and stroke events<sup>19</sup>.

The UK has 200 mg ibuprofen modified release products available OTC, and an 800 mg sustained-release tablet available by prescription.

In the USA, 800 mg ibuprofen prolonged release tablets are available by prescription.

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<sup>14</sup> [Therapeutic Goods Administration Search results](#)

<sup>15</sup> [Database of Adverse Event Notifications - medicines](#)

<sup>16</sup> [Database of Medicine Classifications](#)

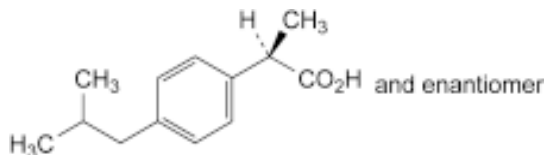
<sup>17</sup> [Notice - Prescription Drug List \(PDL\): Ibuprofen](#)

<sup>18</sup> [Advil Frequently Asked Questions](#)

<sup>19</sup> [Summary Safety Review - Prescription Oral Ibuprofen \(Non-Steroidal Anti-inflammatory Drug\) - Risk of Serious Heart and Stroke Adverse Events at High Doses](#)

### Substance summary

Ibuprofen is a white or almost white, crystalline powder or colourless crystals. It is practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates. The molecular weight of ibuprofen is 206.3, molecular formula  $C_{13}H_{18}O_2$ .



**Figure 1.4: Structure of ibuprofen**

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used as an analgesic, antipyretic, and anti-inflammatory. It decreases synthesis of pain- and inflammation-promoting prostaglandins via non-selective inhibition of both cyclo-oxygenase (COX), COX-1 and COX-2 enzymes. It has been extensively studied, and its efficacy and safety profile in humans following oral administration is well-established.

Numerous oral non-prescription ibuprofen formulations are now available (including tablets, capsules, liquigels, and oral suspension), with various dosage strengths. These 'immediate release' (IR) non-prescription dose forms are indicated for the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders and soft-tissue disorders such as sprains and strains. It is also used to reduce fever. The currently recommended non-prescription ibuprofen oral dose for pain and/or fever in adults is 200 – 400 mg every 4 to 6 hours as needed, with a maximum daily dose of 1200 mg.

### Pre-meeting public submissions

Two (2) submissions were received. Both supported the scheduling proposal. The main points were:

- Ibuprofen has well-characterised safety profile. The rescheduling would be consistent with other comparable analgesic substances and risks are mitigated via the intervention of a pharmacist (i.e. Schedule 3 criteria).
- This proposal aligns with other recent NSAID rescheduling decisions.
- Permitting advertising would have benefits for both consumers and pharmacists with increasing awareness of Schedule 3 medicines in general.

The [public submissions](#) will be made available on the TGA website.

### Summary of ACMS advice to the delegate

The committee advised that the Schedule 3 entry for ibuprofen be amended as follows:

#### Schedule 3 – Amend Entry

##### IBUPROFEN:

- a) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units, when labelled:
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age; **or**
- b) **in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled:**

- i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age,
- except** when included in or expressly excluded from Schedule 2.

## **Appendix H – New Entry**

### **IBUPROFEN**

The committee also recommended an implementation date of **1 October 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- This will give consumers access to a product for pain relief that is longer-lasting than currently available products.
- The potential for abuse and toxicity are low and in line with existing ibuprofen products.
- Pharmacist intervention, CMI and TGA mandated RASML warning statements will assist consumers with managing any risks.
- There is a public health interest to inform consumers about pain relief options through advertising.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to amend the Schedule 3 entry for ibuprofen. The proposed Schedule entry is as follows:

#### **Schedule 3 – Amend Entry**

##### **IBUPROFEN:**

- a) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units, when labelled:
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age; or

- b) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled:
- i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age,
- except** when included in or expressly excluded from Schedule 2.

## **Appendix H – New Entry**

### **IBUPROFEN**

The proposed implementation date is **1 October 2017**.

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 a substance; (b) the purposes for which a substance is to be used 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 of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- This will give consumers access to a product for pain relief that is longer-lasting than currently available products.
- The potential for abuse and toxicity are low and in line with existing ibuprofen products.
- Pharmacist intervention, CMI and TGA mandated RASML warning statements will assist consumers with managing any risks.
- There is a public health interest to inform consumers about pain relief options through advertising.

### ***Public submissions on the interim decision***

One (1) public submission was received which supported the interim decision for ibuprofen.

The main points were:

- Ibuprofen has well-characterised safety profile. The rescheduling would be consistent with other comparable analgesic substances and risks are mitigated via the intervention of a pharmacist (i.e. Schedule 3 criteria).
- Permitting advertising would have benefits for both consumers and pharmacists with increasing awareness of Schedule 3 medicines in general.

### ***Delegate's final decision***

The delegate notes the submission in support of the interim decision and as no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to amend the Schedule 3 entry for ibuprofen. The implementation date is **1 October 2017**.

## 1.5. Flurbiprofen

### *Referred scheduling proposal*

An application was submitted to down-schedule flurbiprofen from Schedule 2 to unscheduled containing 0.25 per cent or less of flurbiprofen or containing 10 mg or less per dose of flurbiprofen when in undivided dosage forms.

### *Current scheduling status*

Flurbiprofen is currently listed in Schedules 4 and 2 as follows:

#### **Schedule 4**

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

#### **Schedule 2**

FLURBIPROFEN in preparations for topical oral use when:

- a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit; or
- b) in undivided preparations containing 0.25 per cent or less, or 10 mg or less per dose, of flurbiprofen.

### *Scheduling history*

Flurbiprofen was first included in Schedule 4 in November 1993. The committee decided to reschedule flurbiprofen in divided preparations for topical oral use containing 10 mg or less of flurbiprofen per dosage unit from Schedule 4 to Schedule 3 in February 2000. Subsequent rescheduling to Schedule 2 for this type of preparation followed in October 2002. The committee's decision was based on post-marketing safety data demonstrating that the preparation had a very low potential for causing adverse effects and no evidence of abuse or misuse.

In February and June 2010, the NDPSC considered an application to reclassify flurbiprofen to unscheduled in lozenges and liquid preparations for topical oral use. Members generally felt that the case for unscheduled access to topical oral flurbiprofen had not been made. Members agreed that there was only a small risk, but this needed to be balanced against little benefit. The committee agreed that preparations of flurbiprofen for topical oral use (10 mg or less) should remain in Schedule 2. The discussion on whether to include undivided preparations in Schedule 2 (and not unscheduled) included: a lack of experience with the use of undivided preparations in Australia; flurbiprofen had been classified as a Category C pregnancy risk and this was not appropriate for an unscheduled product; while there was only a small risk, there was little demonstrated benefit; the risk of idiosyncratic reactions to flurbiprofen. The committee confirmed the February 2010 decision to broaden the Schedule 2 flurbiprofen entry to include undivided preparations containing 0.25 per cent or less or 10 mg or less per dose of flurbiprofen.

### *Scheduling application*

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

#### **Schedule 4 – Proposed Amendment**

FLURBIPROFEN **except** when included **or expressly excluded from** Schedule 2.

#### **Schedule 2 – Proposed Amendment**

FLURBIPROFEN in preparations for topical oral use when:

- a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit; or

b) in undivided preparations ~~containing 0.25 per cent or less, or 10 mg or less per dose, of flurbiprofen except:~~

- i) in preparations containing 0.25 per cent or less of flurbiprofen; or
- ii) in preparations containing 10 mg or less per dose of flurbiprofen.

The applicant's reasons for the request are:

- The proposed rescheduling would allow the sale of throat sprays containing flurbiprofen in retail outlets other than pharmacy.
- Although there are no 'factors' for an 'unscheduled' classification, XXXX meets or exceeds all of the factors for Schedule 2.
- The dose of the non-steroidal anti-inflammatory drug (NSAID) in XXXX is low, at around 15% of the maximum recommended oral dose of flurbiprofen. Systemic exposure is further reduced by relatively low absorption from the oral mucosa of around 10% of the equivalent dose when swallowed.
- NDPSC in February 2010, in relation to a proposal for unscheduled status for flurbiprofen products for topical oral use, "agreed that there was only a small risk, but this needed to be balanced against little benefit".
- The NDPSC's conclusion on risk has been confirmed by the low number of adverse events reported in TGA's Database of Adverse Event Notifications since 2001 and the low incidence of adverse events in relation to cumulative exposure worldwide since 1976.
- In terms of benefit, XXXX containing flurbiprofen 8.75 mg per 0.54 mL actuation was registered in September 2015 following evaluation by TGA. The approved indications are: "For relief of pain, swelling and inflammation associated with severe sore throats".
- Efficacy was further confirmed in a recent study sponsored by the applicant/sponsor (de Looze F 2016) investigating the use of XXXX in adults with sore throat due to upper respiratory tract infection. This study concluded: "Flurbiprofen spray provides rapid and long-lasting relief from sore throat symptoms, and is well-tolerated over three days".
- The currently marketed XXXX products include the standard label warning statements that are required for all NSAIDS, including the small packs of ibuprofen that are available for sale in supermarkets.
- Given the low level of risk associated with flurbiprofen for topical oral use, the mitigation of that risk by appropriate labelling, the accepted efficacy of XXXX for the symptomatic treatment of sore throat and the long-standing acceptance of this condition as being suitable for self-treatment by consumers in a non-pharmacy environment, an 'unscheduled' classification is warranted.

### ***Australian regulatory information***

Currently, in Australia, flurbiprofen products are available as lozenges for the treatment of sore throats (Schedule 2) and eye drops for the treatment of intraoperative meiosis (Schedule 4).

The ARTG has flurbiprofen or its sodium hydrate salt, flurbiprofen sodium dehydrate, as the active ingredient included in 5 registered products associated with two different sponsors. The registered formulations include: 8.5 mg granules; 8.75 mg/0.54 mL throat spray solution pump metered dose aerosol; 0.03% eye drops and 300 microgram/mL eye drops; and 8.75 mg lozenge blister pack.

The current application is referring to 8.75 mg/0.54 mL throat spray solution pump metered dose aerosol.



## International regulations

In the USA, flurbiprofen in eye drops and tablets are prescription medicines<sup>20</sup>. It was first entered as a prescription drug in 1985. No information could be found regarding flurbiprofen as an OTC product in the USA.

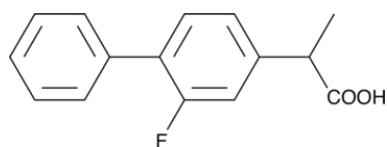
In Canada, flurbiprofen or its salts was entered on the Prescriptions Drugs List in December 2013 as a product for human use.<sup>21</sup>

In New Zealand, flurbiprofen is a prescription product except in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit, which have been pharmacy-only medicines since 2010.<sup>22</sup>

Flurbiprofen lozenges are also marketed in countries including, New Zealand, Italy, Thailand, Poland, Australia, United Kingdom and Ireland as non-prescription medicines. In addition they are also available in several European countries as prescription medicines.

## Substance summary

Flurbiprofen is a non-selective COX inhibitor. It inhibits human recombinant COX-1 and COX-2 with IC<sub>50</sub> values of 0.04 and 0.51 µM, respectively<sup>23</sup>. Flurbiprofen is a white crystalline solid, molecular weight 244.3, molecular formula C<sub>15</sub>H<sub>13</sub>FO<sub>2</sub>. Flurbiprofen is a member of the phenylalkanoic acid derivative family of NSAIDs. It is used in ophthalmic solutions, throat lozenges and throat sprays. Other reported uses include orally for arthritis and dental pain. Pharmacokinetic data indicate greater than 99% protein binding, hepatic metabolism (CYP2C9), with an elimination half-life of 4.7 – 5.7 h and renal excretion.



**Figure 1.5: Structure of flurbiprofen (anhydrous free acid)**

Flurbiprofen is a weak, monoprotic carboxylic acid (pKa 4.2), structurally related to ibuprofen. It has an anti-inflammatory effect when applied directly to the throat (de Looze 2016). Buccal absorption of flurbiprofen is low, with blood levels around 10% of those obtained from the same dose taken orally and swallowed (Gonzales-Younes 1991).

The recommended maximum daily dose of 43.75 mg (5 doses) in the throat spray is less than 15% of the 300 mg maximum recommended daily dose of flurbiprofen for oral ingestion (Martindale November 2016).

## Pre-meeting public submissions

One (1) submission was received and this opposed the scheduling proposal. The main points of the submission were:

- Schedule 2 is appropriate as it gives consumers access to professional advice to enable the determination of the nature and cause of the condition being treated.

<sup>20</sup> [Drugs@FDA: FDA Approved Drug Products](#)

<sup>21</sup> [Prescription Drug List](#)

<sup>22</sup> [Database of Medicine Classifications](#)

<sup>23</sup> J. Barnett, J., *et al.* Purification, characterization and selective inhibition of human prostaglandin G/H synthase 1 and 2 expressed in the baculovirus system. *Biochimica et Biophysica Acta* **1209** 130-139 (1994)

- Unsupervised sales of flurbiprofen would pose unnecessary and preventable risk to consumers, particularly for use in pregnancy, use in children, pre-existing health conditions and interactions with other medications.
- A sore throat may be an indication of a more serious complication and those from demographics at higher risk of developing such complications may require referral to a doctor.

The [public submission](#) will be made available on the TGA website.

### ***Summary of ACMS advice to the delegate***

The committee advised that the current scheduling of flurbiprofen remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- there has been a fatal hypersensitivity reaction.
- although other unscheduled substances are also pregnancy Category C, there is limited experience with this product.
- no public health benefit from availability as unscheduled.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is that the current scheduling of flurbiprofen remains appropriate.

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 a substance; (b) the purposes for which a substance is to be used 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 of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- There has been a fatal hypersensitivity reaction.
- Although other unscheduled substances are also pregnancy Category C, there is limited experience with this product.

- Unsupervised sales of flurbiprofen would pose unnecessary and preventable risk to consumers, particularly for use in pregnancy, use in children, pre-existing health conditions and interactions with other medications.
- No public health benefit from availability as unscheduled.

### ***Public submissions on the interim decision***

Two (2) public submissions were received that opposed the interim decision for flurbiprofen.

The main points were:

- Both submissions suggested that the rescheduling of flurbiprofen would benefit the general public.
- There is no evidence of inappropriate use, misuse or abuse.
- There is only a small risk that a consumer would confuse their condition with a more serious disease/condition.
- Flurbiprofen only carries a small risk and there is limited systemic absorption from the oral mucosa.
- One submission suggestions that the risk of fatal hypersensitivity reaction is extremely low.
- Appropriate warning labels for NSAIDs would reduce the risk of unnecessary and preventable risk to consumers.

### ***Delegate's final decision***

The delegate notes the two submissions not supporting the interim decision but supporting the original application. However, in view of the throat spray product having only been approved in Australia since September 2015 and ongoing monitoring of adverse events occurring with continuing requirements for annual Periodic Safety Update Report (PSUR), it is not appropriate at this time.

The delegate's final decision is that the current scheduling of flurbiprofen remains appropriate.

## **1.6. Penciclovir**

### ***Referred scheduling proposal***

An application was submitted to exempt penciclovir from scheduling in preparations containing 1 per cent or less of penciclovir for the treatment of herpes labialis in packs containing 10 g or less.

### ***Current scheduling status***

Penciclovir is currently included in Schedules 4 and 2 of the Poisons Standard as follows:

#### **Schedule 4**

PENCICLOVIR except when included in Schedule 2.

#### **Schedule 2**

PENCICLOVIR for external use for the treatment of herpes labialis.

### ***Scheduling history***

In August 1996, the NDPSC considered a proposal to include penciclovir in Schedule 3 after registration approval was granted. It was noted that while penciclovir and aciclovir were related drugs and few adverse effects would be expected to be associated with the use of penciclovir, there was no data on adverse effects resulting from the widespread use of penciclovir in topical form. In addition, it

did not appear to be more efficacious than aciclovir and a public need for this particular product had not been demonstrated. The committee considered that Schedule 4 for penciclovir was appropriate, in view of the lack of post-marketing experience with the topical preparation in Australia and the availability of other preparations of similar efficacy and well documented post-marketing history.

In May 1998, the NDPSC considered proposal to reschedule penciclovir from Schedule 4 to Schedule 2 in preparations for the treatment of cold sores (herpes labialis) in preparations containing 1% of penciclovir. The committee agreed that on the basis of market history, another product for treatment of herpes labialis already being in Schedule 2 and the low concern for possible unknown side effects of penciclovir (the active metabolite of famciclovir) that Schedule 2 was appropriate.

In August 1998, the NDPSC agreed that Schedule 2 was appropriate for dermal preparations containing penciclovir. The committee did not consider that there was sufficient justification to require Warning Statement 64 on either aciclovir or penciclovir cold sore creams. Warning statement 64 was recommended to be removed from Appendix F, part 3 for penciclovir and aciclovir at the February 1999 NDPSC meeting.

#### *Relevant scheduling history for related substance, aciclovir*

Current scheduling of aciclovir:

#### **Schedule 4**

ACICLOVIR **except** in preparations containing 5 per cent or less of aciclovir for the treatment of herpes labialis in packs containing 10 g or less.

When compounded with hydrocortisone, aciclovir is Schedule 3 at 5% w/w or less in adults and adolescents (12 years of age and older).

In August 1984, the Poisons Scheduling Standing Committee agreed to place aciclovir in Schedule 4.

In May 1993, the committee considered a request for a change of topical aciclovir scheduling from Schedule 4 to Schedule 3, for an OTC indication, without the product or indication having already been approved by the TGA. The committee declined to consider the application for a drug product which it believed should be evaluated through the appropriate channels.

In May 1996, the NDPSC considered a submission in support of a change from Schedule 4 to Schedule 2 for aciclovir cold sore cream (5% w/w, 2g). The committee noted that when the sponsor had applied for ADEC approval for the indication for "the treatment of herpes simplex viral infection of the lips" that committee had agreed to the indication. The committee agreed to waive the "2 year rule" in view of the fact that aciclovir has been used for many years as an eye ointment in Australia and had been available overseas for many years as a cold sore non-prescription preparation, without giving rise to public health concerns

In August 1997, the NDPSC noted the Australian Approved Name (AAN) change from acyclovir to aciclovir.

In February 1999, the NDPSC endorsed amendment of the Schedule 2 entry to read: 'ACICLOVIR FOR EXTERNAL USE FOR THE TREATMENT OF HERPES LABIALIS'.

In 2001 – February 2002, the NDPSC considered the proposal to exempt preparations containing 5% or less of aciclovir for dermal use from the requirements of scheduling. The committee agreed to exempt dermal preparations containing aciclovir for use in the treatment of cold sores from the requirements of scheduling with appropriate pack size restriction which accommodated existing Schedule 2 products.

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

consumers. In addition, the product was simple to use and increased access to such a product would be beneficial to public health.

In October 2002, the NDPSC considered the NZ MCC recommendations to harmonise aciclovir and decided that it should remain unharmonised and be placed on the 2-year review list of unharmonised substances.

In March 2015, the ACMS reconsidered the scheduling of hydrocortisone when compounded with aciclovir, in relation to a proposed Schedule 3 amendment and Appendix H listing. The committee recommended that it was not necessary to include aciclovir in Appendix H as topical aciclovir has been exempt from scheduling for over a decade without signals indicating significant risk at this scheduling level. The Schedule 3 entry for hydrocortisone and hydrocortisone acetate was amended in October 2015 for human therapeutic use containing 1 per cent of hydrocortisone for dermal use in packs containing 2 g or less of such preparations, containing no therapeutically active constituent other than aciclovir (5% w/w or less) in adults and adolescents (12 years of age and older).

*Relevant scheduling history for related substance, famciclovir*

Current scheduling of famciclovir:

#### **Schedule 4**

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

#### **Schedule 3**

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

The related substance famciclovir is an oral pro-drug that is converted to penciclovir in vivo. In June 1994, ADEC recommended approval for the registration of famciclovir for the treatment of herpes zoster [shingles] infection. In May 1995, the NDPSC agreed to include famciclovir in Schedule 4.

The TGA approved famciclovir for the treatment of recurrent herpes labialis (cold sores) in January 2007. The approved dosage was 1500 mg administered orally either as a single dose or 750 mg twice daily at 12 hourly intervals (to a total dose of 1500 mg per episode). Famciclovir is also indicated in immune compromised patients for the treatment of uncomplicated herpes zoster (shingles), and treatment and prophylaxis of herpes labialis.

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

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

In May 2009, the New Zealand MCC rejected a submission to reclassify famciclovir 500 mg tablets from prescription medicine to restricted (pharmacist only) medicine. Subsequently, at its November 2009 meeting, the MCC reconsidered the submission with further information on warnings and training material relating to use in immunocompromised patients. The MCC agreed to reclassify famciclovir

500 mg tablets to restricted (pharmacist only) medicine in packs of 3 tablets for the treatment of recurrent herpes labialis.

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

In October 2011 the ACMS again considered a proposal to down-schedule famciclovir to Schedule 3. The committee noted that the potential for development of resistance had been sufficiently addressed, since famciclovir is not activated into penciclovir until taken into cells infected with the virus. The proposed single (divided) oral dose was considered acceptable and would be beneficial when the use of topical formulation would not be appropriate (i.e. around the eyes). The committee agreed to down-schedule famciclovir to Schedule 3 for oral use, in divided preparations, containing a total dose of 1500 mg or less of famciclovir for the treatment of herpes labialis (cold sores). This was implemented in 2012.

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

#### **Schedule 4 – Proposed Amendment**

PENCICLOVIR ~~except included in Schedule 2~~ in preparations containing 1 per cent or less of penciclovir for the treatment of herpes labialis in packs containing 10 g or less.

#### **Schedule 2 – Delete entry**

~~PENCICLOVIR for external use for the treatment of herpes labialis.~~

#### **Index – Proposed Amendment**

##### **PENCICLOVIR**

Schedule 4

~~Schedule 2~~

The applicant's reasons for the request are:

- It is estimated that up to a third of the world's population are affected by herpes simplex at some stage in their life, with the majority of infections presenting as repeated vesicular eruptions, herpes labialis within the general community. While herpes labialis is self-limiting and will generally resolve within 7-8 days, it can significantly decrease quality of life of those with active or recurrent infections as it can be painful, emotionally distressing and highly contagious. Historically, penciclovir has been used to treat herpes labialis topically, successfully promoting faster resolutions and a reduction in pain.
- Topical cold sore treatments are commonly used by consumers after self-diagnoses of their condition, as already occurs with topical aciclovir. Penciclovir, an alternate option for recurrent cold sore sufferers, is in many respects similar to aciclovir, with benefits in improved healing time and associated pain. As a major difference with aciclovir, available as a 5% topical formulation, penciclovir topical products are formulated at 1%, and although less concentrated they still retain an effective therapeutic outcome due to their greater activity, exclusive towards infected cells
- Penciclovir is indicated only for short term topical use. The product is intended to be applied at two hourly intervals, at least six times a day for up to four days as stated on labelling and packaging. The nature of the product indication is self-limiting. The mean duration of recurrences is 7–8 days, but individual episodes of up to 15 days have been reported. As for aciclovir, it has a

low risk of masking a serious disease, compromising the medical management of a disease, or resulting in a consumer mistaking a cold sore for a more serious condition. With an indicated time frame for product use of 4 days, any misdiagnosis would not significantly delay any referral to a healthcare professional. In addition to an excellent well-defined safety profile, penciclovir is a topical application with no known risk of misuse and abuse; it has high selectivity to viral cells; and low bioavailability / toxicity to human cells, making this medicine a good candidate for reclassification in line with aciclovir topical products

- Reclassification of penciclovir topical would increase the availability of the product to the general community, and act as an alternative to aciclovir topical allowing consumers a greater freedom of choice. Reclassification would also be beneficial for immediate and early access to treatment, since penciclovir is effective at every stage of herpes labialis cycle, from tingle, to blister, to providing potential for early symptom relief regardless of the stage of the condition. With greater access and quicker healing, the virus will be less likely to be transmitted to others, potentially reducing spread and minimising frequency of occurrence.
- Aciclovir, a similar anti-viral agent indicated for the same condition, was reclassified in 2002 from Schedule 2 to Unscheduled, on the basis that the product was safe, simple to use and increased access would be beneficial to the general public. Since aciclovir is no longer a scheduled product when used topically for herpes labialis, it would be logical for both penciclovir and aciclovir to be similarly scheduled and equally accessible to the consumer.

### ***Australian regulatory information***

There is one registered product in Australia that contains penciclovir which is indicated for the treatment of recurrent cold sores (herpes labialis) in adults and children aged 12 years and over.

### ***International regulations***

In New Zealand penciclovir is considered Prescription, except for external use for the treatment of herpes labialis, and it is a pharmacy only medicine for external use for the treatment of herpes labialis<sup>24</sup>. The NDPSC was advised in November 1996 that penciclovir cream was given a Schedule 2 classification in New Zealand.

In the USA, penciclovir is marketed as a prescription 1% topical cream.<sup>25</sup>

In Canada, penciclovir is marketed as a prescription 1% topical cream.<sup>26</sup>

No reference to penciclovir has been provided for in S26BB, as penciclovir is a scheduled ingredient and not eligible for use in listed medicines<sup>27</sup>.

### ***Substance summary***

Penciclovir is a synthetic guanine derivative, chemically designated as 9-[4-hydroxy-3-(hydroxymethyl)butyl] guanine. It is a white to pale yellow crystalline solid with a molecular weight of 253.3 g/mol.

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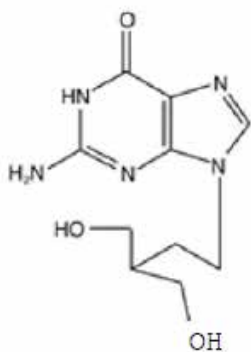
<sup>24</sup> [Database of Medicine Classifications](#)

<sup>25</sup> [Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations](#)

<sup>26</sup> [Prescription Drug List](#)

<sup>27</sup> [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#)





**Figure 1.6: Structure of penciclovir**

Penciclovir has inhibitory activity against herpes simplex virus (HSV) types 1 and 2. It targets virus-infected cells where it is rapidly converted into penciclovir-triphosphate (mediated via virus-induced thymidine kinase), which inhibits viral DNA polymerase by competition with deoxyguanosine triphosphate and is incorporated into the extending DNA chain, preventing significant chain elongation. Consequently, viral DNA synthesis and therefore viral replication are inhibited.

Penciclovir is only readily phosphorylated in virus-infected cells. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable.

The active penciclovir triphosphate has a half-life of up to 10-20 hours, remaining active in infected cells for up to 12 hours.

#### *Toxicity*

Both penciclovir and aciclovir have a similar mechanism of action and a long history of use. Penciclovir has minimal side effects with the majority of adverse effects being at the site of application including, erythema, itching and contact dermatitis.

The applicant noted that the safety profile of aciclovir and penciclovir are fundamentally similar and for more than 20 years aciclovir use has been considered safe and well tolerated regardless of the administration route. A good safety profile of penciclovir cream has been reported in two large clinical trials. Penciclovir is poorly absorbed following oral administration. Systemic absorption is negligible and adverse effects are similar to those observed with placebo.

In the event of accidental oral ingestion or over-dosage, no untoward effects would be expected if the entire contents (2 g) of penciclovir 1% cream were ingested and no specific treatment is necessary. Some irritation of the mouth could occur.

#### ***Pre-meeting public submissions***

One (1) submission was received, which opposed the scheduling proposal. The main points in the submission were:

- The current scheduling remains appropriate due to best practice being a certain level of professional intervention.
- Broader access to immunocompromised individuals may contribute to drug resistance.

The [public submission](#) will be made available on the TGA website.

#### ***Summary of ACMS advice to the delegate***

The committee advised that the Schedule 2 entry for PENCICLOVIR be deleted and that the Schedule 4 entry be amended as follows:

#### **Schedule 4 –Amend Entry**



PENCICLOVIR ~~except when included in Schedule 2~~ in preparations containing 1 per cent or less of penciclovir for the treatment of *herpes labialis* in packs containing 10 g or less.

#### **Schedule 2 – Delete Entry**

~~PENCICLOVIR for external use for the treatment of herpes labialis.~~

#### **Index – Amend Entry**

#### **PENCICLOVIR**

Schedule 4

~~Schedule 2~~

The committee also recommended an implementation date of **1 October 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice comprised the following:

- Low toxicity
- Sufficient data available to demonstrate use of the product in its current presentation
- Public health benefit of increased access
- Penciclovir has a similar safety profile and precautions as unscheduled topical aciclovir

#### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

#### ***Delegate's interim decision***

The delegate's interim decision is to delete the Schedule 2 entry and amend the Schedule 4 entry for penciclovir. The proposed Schedule entry is as follows:

#### **Schedule 4 – Amend Entry**

PENCICLOVIR **except** in preparations containing 1 per cent or less of penciclovir for the treatment of *herpes labialis* in packs containing 10 g or less.

#### **Schedule 2 – Delete Entry**

#### **Index – Amend Entry**

#### **PENCICLOVIR**

## Schedule 4

The proposed implementation date to amend the Schedule 4 entry is **1 October 2017**.

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 a substance; (b) the purposes for which a substance is to be used 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 reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Low toxicity.
- Sufficient data available to demonstrate use of the product in its current presentation.
- Public health benefit of increased access.
- Penciclovir has a similar safety profile and precautions as unscheduled topical acyclovir.

### ***Public submissions on the interim decision***

No public submissions were received in response to the interim decision for penciclovir.

### ***Delegate's final decision***

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

The delegate's final decision is to delete the Schedule 2 entry and amend the Schedule 4 entry for penciclovir. The implementation date is **1 October 2017**.

## **1.7. Loratadine**

### ***Referred scheduling proposal***

An application was submitted to exempt loratadine from scheduling when 10 mg or less in divided preparations for oral use in packs containing not more than 5 dosage units when used in children 6 - 12 years of age for the treatment of seasonal allergic rhinitis.

### ***Current scheduling status***

Loratadine is in Schedules 4 and 2, and in Appendix F, Part 3 of the Poisons Standard as follows:

#### **Schedule 4**

LORATADINE **except**:

- a) when included in Schedule 2; or
- b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over, when:
  - i) in a primary pack containing 10 dosage units or less; and
  - ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

#### **Schedule 2**

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

- a) in a primary pack containing 10 dosage units or less; and
- b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

### **Appendix F, Part 3**

ANTI-HISTAMINES not separately specified in this Appendix **except**:

- a) dermal, ocular, parenteral and paediatric preparations;
- b) oral preparations of astemizole, desloratadine, fexofenadine, loratadine or terfenadine;
- c) nasal preparations of azelastine; or
- d) preparations for the treatment of animals

Warning statements: 39 (This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol) or 40 (This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery).

### ***Scheduling history***

At the May 1992 NDPSC meeting, the committee recommended Loratadine be included in Schedule 4.

In November 1992 the NDPSC declined to down schedule loratadine to Schedule 3 due to concerns about cardiac side effects.

In April 1994, the NDPSC rescheduled loratadine tablets to Schedule 3.

In November 1995, the NDPSC rescheduled loratadine syrup to Schedule 3.

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

In August 1997 meeting, the NDPSC confirmed the current Schedule 3 entry.

Loratadine, cetirizine and fexofenadine were included in Appendix H in August 1998.

In February 1999, the NDPSC considered the rescheduling of loratadine from Schedule 3 to Schedule 2. The NDPSC agreed that loratadine in preparations for oral use should be rescheduled, and that the restriction to '*only therapeutically active ingredient*' should no longer apply.

In November 1999, the NDPSC supported a recommendation from the Trans-Tasman Harmonisation Working Party (TTHWP) that on the grounds of harmonisation cetirizine in preparations for oral use be rescheduled from Schedule 3 to Schedule 2. As a consequence of the deletion of the Schedule 3 entry was the deletion of the Appendix H (Schedule 3 Poisons permitted to be advertised) entry.

In October 2005, the NDPSC agreed to alter the wording of Appendix F Part 3 and remove cetirizine for oral use (except when included in Schedule 2) from Appendix K of the Poisons Standard. As the balance of current evidence indicates that cetirizine is no more sedating than loratadine.

In February 2012, the Advisory Committee of Medicines Scheduling recommended exempting from scheduling oral preparations containing 10 mg or less of loratadine in packs containing not more than five dosage units for the treatment of seasonal allergic rhinitis in adults and children over the age of 12 years. The scheduling delegate agreed with the ACMS advice, and implemented this decision on 22 November 2012.

In July 2013, the ACMS considered a proposal to reschedule loratadine from Schedule 2 to unscheduled in oral preparations containing 10 mg or less in packs containing not more than 5 daily doses for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and over, with a warning label recommending a daily dose not exceeding 10 mg loratadine for adults and children with body weight over 30 kg, or recommended daily dose not exceeding 5 mg loratadine for children with body weight 30 kg and under. The committee recommended that the current scheduling of loratadine remained appropriate, due to the risk of inappropriate use and delay in correct diagnosis, the lack of data on adverse effects/experiences/poisoning in Australia, no substantial public health benefit in exempting from schedules and a complicated dosage regimen with risk of inappropriate dosing.

In March 2016, the ACMS considered the proposal to amend the schedule entries to increase the pack size of exempted loratadine from five dosage units to 10 dosage units. The scheduling delegate agreed with the advice from the ACMS and set an implementation date of 1 October 2016.

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

#### **LORATADINE ~~except:~~**

- a) when included in Schedule 2; or
- b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis ~~in adults and children 12 years of age and over~~ when:
  - i) in a primary pack containing 10 dosage units or less; ~~and~~ **for children 12 years and over;**  
**or**
  - ii) ~~labelled with a recommended daily dose not exceeding 10 mg of loratadine.~~
- c) **in a primary pack containing 5 dosage units or less when labelled for children 6-12 years; and**
  - i) **labelled with a recommended daily dose not exceeding 10 mg loratadine for adults and children over 9 years of age; and**
  - ii) **labelled with a recommended daily dose not exceeding 5 mg.**

#### **Schedule 2 – Proposed Amendment**

LORATADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis when:

- a) in a primary pack containing 10 dosage units or less when labelled for children 12 years and over; ~~and~~ **or**
- b) ~~labelled with a recommended daily dose not exceeding 10 mg of loratadine~~ **in a primary pack containing 5 dosage units or less when labelled for children 6–12 years; and**
  - i) **labelled with a recommended daily dose not exceeding 10 mg of loratadine for adults and children over 9 years of age; and**
  - ii) **labelled with a recommended daily dose not exceeding 5 mg loratadine for children 6-9 years of age.**

The applicant's reasons for the request are:

- Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation, with symptoms of nasal drainage, nasal congestion, sneezing and/or nasal itching. Allergic rhinitis is a common

condition affecting children. In Australia, about 12-20% of children aged 6-14 years are affected and the prevalence could be up to 35-47% in some areas. Allergic rhinitis significantly impacts the health and quality of life in children and their carers. It reduces school attendance, impairs cognitive functioning and reduces learning ability and represents a large public health burden associated with significant healthcare costs.

- Allergic rhinitis is readily self-diagnosed by consumers and can be seasonal or perennial. SAR is caused by an IgE-mediated reaction to seasonal aeroallergens such as pollens. This reaction leads to typical symptoms such as sneezing and nasal congestion and is readily able to be identified. Most Australian adults now self-medicate for allergic rhinitis. The diagnosis and treatment of allergic rhinitis in children follows essentially the same pattern as that in adults other than in children younger than 2 years who may be referred to an allergist/immunologist for diagnosis and subsequent management. An April 2015 XXXX consumer study shows that Australian consumers purchase loratadine products for self-treatment including parents and carers who buy products for children.
- Second generation non-sedating antihistamines including loratadine, fexofenadine and cetirizine have been proven efficacious and safe for the control of SAR and are recommended as first line treatment for mild to moderate allergic rhinitis in both adults and children. To date in Australia, second generation non-sedating antihistamines are only available for children 12 years and over outside of pharmacies. This leaves an entire class of efficacious and safe medications unavailable for children under 12 years of age other than via pharmacy. This is in contrast to similar countries such as the UK and the USA where these medications have been freely accessible outside of pharmacies for children 2 years and over for more than 10 years.
- Loratadine is one of the leading second generation non-sedating antihistamines and is widely regarded as a safe and efficacious treatment for the symptoms of allergic rhinitis in children 12 months of age and over. Loratadine as an effective first line treatment for the symptoms of seasonal allergic rhinitis has been available for children 12 months and over in Australia since 1992, and it has been available as an unscheduled medicine in small packs of 5 tablets and capsules for children 12 years and over since 2012. With a long history of use in young children in Australia, access to loratadine only via pharmacy for children under 12 years of age presents a gap in access for affected children and their carers.
- Access to medicines can be restricted in terms of location and opening hours of community pharmacies in Australia. Non-pharmacy outlets such as supermarkets and local convenience stores are generally more accessible as there are many more outlets available, and they generally operate over longer trading hours. It is convenient for consumers to purchase a product suitable for their minor health condition from supermarkets or other convenience stores rather than only in pharmacies, especially for fast relief of symptoms. Increased access of a second generation non-sedating antihistamine like loratadine for children under 12 years of age outside of pharmacies will assist parents and carers and improve public health outcomes.
- The symptoms of SAR typically appear during the hay fever season when aeroallergens are abundant. The length of seasonal exposure to these aeroallergens is dependent on geographic location and climatic conditions, and can last for several months of the year in Australia. The flexibility of the antihistamine treatment loratadine which is used on an 'as needed' basis provides convenient self-medication during the hay fever season, especially for those with episodic or intermittent symptoms which may be triggered by the aeroallergens at any time during the season and last for weeks. Loratadine, with minimal toxicity compared to other medications, is an ideal candidate for rescheduling to an unscheduled medicine in a small pack of 5 dosage units for episodic treatment of symptoms in younger children during the hay fever season.
- The symptoms of SAR are easily recognised because of the rapid and reproducible onset and offset in association with pollen exposure, which are not likely to be indicative of a more serious underlying diagnosis. The seasonal nature of the symptoms leads to easy recognition by sufferers and carers, largely negating the need for professional advice. The rescheduling of loratadine from

Schedule 2 to unscheduled in 2012 has shown that the risks of misdiagnosis or masking of underlying diseases are minimal. The proposed unscheduled loratadine products for children 6-12 years of age will retain the same label statements as the existing loratadine unscheduled product for use in children 12 years and over and will contain the same medical and safety information to ensure the safe use of the medication outside of pharmacies is continued in this age group. XXXX also proposes to include an additional label statement to the effect of 'Do not use this product when experiencing first-time hay fever symptoms without advice from a healthcare professional' to minimise any potential risk of misdiagnosis or delay in diagnosis in this particular age group.

- Loratadine is considered to be a 'second generation non-sedating antihistamine' with an excellent safety profile. The toxicity and safety of loratadine has been well established with over more than 20 years of use in Australia and internationally including use in children as young as 12 months of age.
- Loratadine has a safety profile similar to that of placebo, does not potentiate the CNS effects of alcohol or diazepam and there have been no reports of clinically significant interactions between loratadine and drugs such as erythromycin, cimetidine and ketoconazole. Loratadine has a similar safety profile in children; the incidence of loratadine associated adverse effects in children appears to be similar to placebo.
- Loratadine has a wide therapeutic index with no unusual neurological symptoms or signs of toxicity in cases of accidental overdose. In volunteer studies, single doses of loratadine up to 160 mg were administered without any untoward effects. Loratadine is not associated with cardiovascular toxicity. Children who accidentally ingest large quantities of loratadine (up to 40 mg) have tolerated this well and can be adequately managed at home.
- Loratadine is generally safe for use in children 12 months of age and older. The types and frequencies of adverse events reported in children are consistent with those reported in adults with no increased risks identified in children. Only a few adverse events in children have been reported in Australia. The availability of unscheduled loratadine products in Australia since 2012 has not resulted in any safety concerns, providing confidence that the quality use of loratadine for children 6-12 years purchased in non-pharmacy outlets in small packs can be achieved by appropriate labelling and packaging.
- A simple age-based dosing instruction for children is proposed to ensure easy administration to children without healthcare professional advice. Current Schedule 2 loratadine medicines marketed for children in the age group of 6-12 years has an age and body weight based dosing instruction (10 mg for children 2 years and over with a body weight over 30 kg, and 5 mg for children 2-12 years of age with a body weight up to 30 kg). In a previous submission to the ACMS in July 2013, this age and body weight dosing regime was deemed too complicated for self-medication without healthcare professional assistance. Age-only dosing instructions, which are based on the evidence that the average Australian child with a body weight of 30 kg is around 9.5 years of age is proposed to ensure that the dosing is effective and safe and dosing instructions are clear and can be followed by parents and carers easily without professional advice. Proposed dosage instructions are as follows: Children 6-9 years: 1 tablet once daily as necessary Children 9-12 years and Adults: 2 tablets once daily as necessary. The proposed labelling will also state "Do not use more than the recommended dose".
- Given the evidence that loratadine has a well-established safety profile, and the risk of misuse and inappropriate use is rare, it is considered that an unscheduled pack size containing 5 dosage units of loratadine for children 6-12 years of age presents minimal risk to children while increasing the availability of an efficacious second generation non-sedating antihistamine.
- In countries with a similar regulatory system to Australia such as the UK and the USA, loratadine has been available for many years for children as an unscheduled medicine at a much younger age (2 years and over) with wider therapeutic indications SAR, perennial allergic rhinitis and chronic urticaria) with either no pack size restrictions or in larger pack sizes than in Australia. In the USA,

loratadine in both solid and liquid forms is approved in OTC medications (equivalent to unscheduled medicines in Australia) for children 2 years and over without any pack size limitations. In the UK both solid and liquid forms of loratadine have been approved for children 2 years and over in large pack sizes (tablets 30 packs; liquids 70 mg) since 2012.

### ***Australian regulatory information***

The Australian Register of Therapeutic Goods (ARTG<sup>28</sup>) has fifty (50) entries for products containing loratadine listed. The products are marketed towards both adults and children's use and come in a range of dosage forms including, 1 mg/1 mL liquid (flavoured), 10 mg tablets and capsules, 5 mg chewable tablets, 10 mg orally disintegrating tablet and 10 mg liquid capsules. In addition there are combination products such as loratadine 5 mg with 120 mg pseudoephedrine sulphate.

A search on the Database of Adverse Event Notifications list (DAEN) for dates between January 1992 and August 2016 returned 815 reported cases of adverse events related to loratadine. 710 of the cases were from a single suspected medicine. Four (4) cases were reported to have resulted in death from cardiac arrest (1), hypoxia (1), haematuria (1), and electrocardiogram abnormal (1).<sup>29</sup>

No reference to loratadine has been provided for in S26BB, as loratadine is a scheduled ingredient and not eligible for use in listed medicines.<sup>30</sup>

### ***International regulations***

Globally, loratadine-containing products are marketed in over 110 countries as a safe and effective non-sedating antihistamine for the treatment of allergic rhinitis and allergic skin disorders for adults and children.

Loratadine is available OTC in many countries. In 2 countries (Italy and Czech Republic) there is a pack size limit of 7 days' supply while in others the pack size limit is 10, 14, 30, 70 or unlimited.

In the UK, loratadine tablets have been available as an unscheduled medicine since 2002 in packs containing 7 dosage units for the symptomatic relief and treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children. The current unscheduled pack size limit for loratadine tablets is 30 dosage units when used for the symptomatic relief and treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children 2 years and over and weighing more than 30 kg. Liquid dosage forms are also available unscheduled for children 2 years and over with a pack size limit of 70 mg.

In the USA, loratadine was first approved for OTC use (equivalent to unscheduled in Australia) in 2002 in tablet (including orally disintegrating tablets) and syrup forms for children 2 years and over for hay fever or other upper respiratory allergies without pack size limitations. In 2006, loratadine in chewable tablets and orally disintegrating tablets (5 mg) was further approved for OTC use for when used in children 2 years and over for the symptoms of hay fever or other upper respiratory allergies without pack size limitation.

Health Canada list 17 loratadine products in various dose rapid dissolve 5mg, 10 mg liquid capsule, tablets, capsules and 0.5 mg / mL oral syrup<sup>31</sup>.

The New Zealand Medicines Classification Committee (MCC) at its November 2011 meeting recommended that loratadine be reclassified as a general sale (exempt from scheduling). Medsafe New

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<sup>28</sup> [Therapeutic Goods Administration Search results](#)

<sup>29</sup> [Database of Adverse Event Notifications - medicines](#)

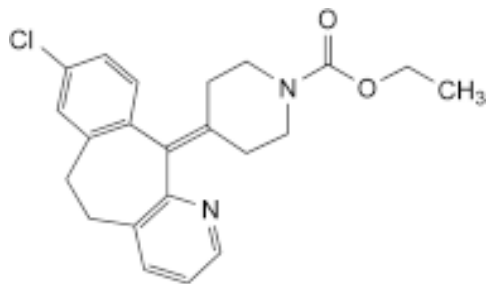
<sup>30</sup> [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#)

<sup>31</sup> [hDetails for: ACTIVELE LD](#)

Zealand regulates loratadine<sup>32</sup> in 10 mg oral divided solid dosage forms as general sale in pack sizes under 10 day supply, other oral dose forms are pharmacy medicines containing not more than 10 day supply. Products outside these restrictions are prescription products.

### **Substance summary**

Loratadine is a white to off-white crystalline powder. It is freely soluble in methanol, ethanol and chloroform, soluble in ether and practically insoluble in water. The molecular weight of loratadine is 352.9, molecular formula C<sub>22</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub>.



**Figure 1.7: Structure of loratadine**

Loratadine is a potent, long-acting tricyclic antihistamine with selective peripheral H<sub>1</sub>-receptor antagonistic activity. Its efficacy as a first line treatment for the symptomatic treatment of allergic rhinitis and allergic skin conditions such as urticaria (hives) has long been established. This once a day treatment for effective control of allergic rhinitis has been available in Australia and globally for more than 20 years. Loratadine has a rapid onset of action after oral administration, usually within one hour. Loratadine is well absorbed with peak plasma levels occurring at approximately 1-2 hours after dosing, and undergoes extensive first-pass metabolism to the active metabolite desloratadine and is then excreted in urine (~40%) and faeces (42%) in a 10 day period. Renal impairment has no significant effect on loratadine clearance.

Loratadine exhibits greater affinity for peripheral H<sub>1</sub>-receptors than for central H<sub>1</sub>-receptors, and loratadine and its metabolites do not readily cross the blood-brain barrier. These properties account for its lack of sedation compared to first generation antihistamines.

Once daily administration of loratadine at therapeutic doses, with or without erythromycin, does not induce adverse cardiac effects in children 5-12 years. No regulatory action has been taken world-wide since the launch of loratadine due to safety concerns. Safety data contained in Periodic Safety Update Reports (PSURs) demonstrates the overall benefit-risk balance for loratadine in children continues to be positive.

### **Pre-meeting public submissions**

Three (3) submissions were received.

*One (1) supported the scheduling proposal. The main points were:*

- Loratadine has safety profile consistent with other similar substances on the market.

*Two (2) did not support the scheduling proposal. The main points were:*

- The proposition is not in the public interest for loratadine to be used in children under general retail availability.
- Loratadine can have sedative-like effects. With the use of higher-than-recommended doses, there is an increased risk of impaired acuity and drowsiness, particularly in young children. Inappropriate use may result without professional advice.

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<sup>32</sup> [Database of Medicine Classifications](#)



- The availability of different pack sizes based on age may cause confusion to consumers.

The [public submissions](#) will be made available on the TGA website.

### ***Summary of ACMS advice to the delegate***

The committee advised that loratadine be exempt from scheduling in preparations containing loratadine 10 mg or less in divided preparations for oral use in packs containing not more than 10 dosage units when used in children 6 years of age for the treatment of seasonal allergic rhinitis.

#### **Schedule 4 – Amend Entry**

LORATADINE **except**:

- a) when included in Schedule 2; or
- b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children ~~6~~<sup>12</sup> years of age and over, when:
  - i) in a primary pack containing 10 dosage units or less; and
  - ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

#### **Schedule 2 – Amend Entry**

LORATADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis when:

- a) in a primary pack containing 10 dosage units or less when labelled for children ~~6~~<sup>12</sup> years and over; and
- b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

The committee also recommended an implementation date of **1 October 2017**.

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

The reasons for the advice comprised the following:

- Loratadine for children has been available at the general sales level in both UK and USA since 2002, without increased adverse events.
- Adults should be able to identify seasonal allergic rhinitis based on symptoms. Symptoms in children are no different to symptoms in adolescents or adults, for whom loratadine is already exempt from scheduling.
- There are risks of delay in correct diagnosis in the younger age group, however risk of adverse outcomes as a result are relatively low, and there is a public health benefit in wider availability of a first line treatment for allergic rhinitis in children.
- The risks can be limited by placing restrictions on the number of days of supply or number of units to an appropriate pack size and appropriate labelling.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal

- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to exempt loratadine from scheduling in preparations containing loratadine 10 mg or less in divided preparations for oral use in packs containing not more than 10 dosage units when used in children 6 years of age and over for the treatment of seasonal allergic rhinitis.

The proposed Schedule entry is as follows:

#### **Schedule 4 – Amend Entry**

LORATADINE **except**:

- a) when included in Schedule 2; or
- b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and over, when:
  - i) in a primary pack containing 10 dosage units or less; and
  - ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

#### **Schedule 2 – Amend Entry**

LORATADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis when:

- a) in a primary pack containing 10 dosage units or less when labelled for adults and children 6 years and over; and
- b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

The proposed implementation date is **1 October 2017**.

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 a substance; (b) the purposes for which a substance is to be used 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 (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Loratadine for children has been available at the general sales level in both UK and USA since 2002, without increased adverse events.
- Adults should be able to identify seasonal allergic rhinitis based on symptoms. Symptoms in children are no different to symptoms in adolescents or adults, for whom loratadine is already exempt from scheduling.

- There are risks of delay in correct diagnosis in the younger age group, however risk of adverse outcomes as a result are relatively low, and there is a public health benefit in wider availability of a first line treatment for allergic rhinitis in children.
- The risks can be limited by placing restrictions on the number of days of supply or number of units to an appropriate pack size and appropriate labelling.

#### ***Public submissions on the interim decision***

One (1) public submission was received which supported the delegate's interim decision for loratadine.

The main points were:

- Loratadine has safety profile consistent with other similar substances on the market.
- Symptoms of seasonal allergic rhinitis are easily identified and can be safely managed by consumers without the need for healthcare professional intervention.

#### ***Delegate's final decision***

The delegate notes the submission which supported the interim decision, and as no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to exempt loratadine from scheduling in preparations containing loratadine 10 mg or less in divided preparations for oral use in packs containing not more than 10 dosage units when used in children 6 years of age and over for the treatment of seasonal allergic rhinitis. The implementation date is **1 October 2017**.

## 2. Joint meeting of the Advisory Committee on Chemicals and Medicines Scheduling (ACCS/ACMS #15)

### Summary of delegate's final decisions

Substance	Final decision
<i>N</i> -(alkylamino) cyclohexylbenzamides (opioids)	<p><b>Schedule 9 – New Entries</b></p> <p><i>N,N</i>-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES <b>except</b> when separately specified in these Schedules.</p> <p><i>N,N</i>-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES <b>except</b> when separately specified in these Schedules.</p> <p>3,4-DICHLORO-<i>N</i>-[(1<i>R</i>,2<i>R</i>)-2-(DIMETHYLAMINO)CYCLOHEXYL]-<i>N</i>-METHYLBENZAMIDE (U-47700).</p> <p><b>Index – Proposed New Entries</b></p> <p><b><i>N,N</i>-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES</b> cross reference: 3,4-DICHLORO-<i>N</i>-[(1<i>R</i>,2<i>R</i>)-2-(DIMETHYLAMINO)CYCLOHEXYL]-<i>N</i>-METHYLBENZAMIDE *(U-47700)</p> <p>Schedule 9</p> <p><b><i>N,N</i>-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES</b> Cross reference: 3,4-DICHLORO-<i>N</i>-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL}BENZAMIDE *(AH-7921)</p> <p>Schedule 9</p> <p><b>3,4-DICHLORO-<i>N</i>-[(1<i>R</i>,2<i>R</i>)-2-(DIMETHYLAMINO)CYCLOHEXYL]-<i>N</i>-METHYLBENZAMIDE (U-47700)</b> cross reference: <i>N,N</i>-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES</p> <p>Schedule 9</p> <p><i>The implementation date is 1 October 2017.</i></p>
<i>In Vitro</i> Diagnostic and Analytical Preparations	The delegate's final decision is that the current inclusion in Appendix A (General Exemptions) of 'IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS' containing 0.001 per cent or less of a poison included in Schedules 1 to 8 remains appropriate.
Sodium <i>a</i> -olefin sulfonates	The delegate's final decision is that no scheduling entry be created for sodium <i>a</i> -olefin sulfonate and sodium alkyl sulfate.

## 2.1 *N*-(alkylamino) cyclohexylbenzamides (opioids)

### *Referred scheduling proposal*

An application was initiated by the delegate to seek advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) to include a new class entry for *N*-(alkylamino)cyclohexylbenzamides in Schedule 9, except when separately specified in these schedules.

### *Current scheduling status and relevant scheduling history*

3,4-Dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide, **U-47700**, is not currently scheduled and there is currently no class entry for *N*-(alkylamino)cyclohexylbenzamides.

A scheduling history is not available for U-47700 or for *N*-(alkylamino)cyclohexylbenzamides as a class since these have not been previously considered for scheduling.

The **related structural isomer** 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide, **\*AH-7921**, is currently listed in Schedule 9 under the entry:

#### **Schedule 9**

3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYLBENZAMIDE \*(AH-7921).

It was placed in Schedule 9 in June 2014 following reported deaths in Sweden and increased use of the substance in Australia through monitoring of Australian internet forums, as well as claims that the substance has no legitimate therapeutic use. The [final scheduling decision for AH-7921](#) was published on the TGA website in May 2014.

### *Scheduling application*

Delegate-initiated application

The delegate's proposed amendment to the Poisons Standard is as follows:

#### **Schedule 9 – Proposed New Entry**

***N*-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES** except when separately specified in these Schedules.

#### **Index – Proposed New Entries**

**3,4-DICHLORO-*N*-[(1*R*,2*R*)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE \*(U-47700)**

cross reference: ***N*-(ALKYLAMINO)CYCLOBENZAMIDES**

#### **Schedule 9**

***N*-(ALKYLAMINO)CYCLOBENZAMIDES**

cross reference: 3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL}BENZAMIDE \*(AH-7921)

#### **Schedule 9**

The delegate's reasons for the scheduling proposal are:

- Safety concerns have been raised that *N*-(alkylamino)cyclohexylbenzamides (such as 3,4-dichloro-*N*-[(1*R*,2*R*)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide, **U-47700**) are being abused overseas, and pose a public health risk, requiring restrictions on their use. U-47700 is a novel synthetic opioid that was recently placed in Schedule 1 by the US Drug Enforcement Administration (DEA), following association with morbidity (46 confirmed deaths in the USA) and abuse parallels with that of heroin, prescription opioids and other novel opioids. US enforcement agencies have found these substances in counterfeit tablets mimicking pharmaceutical opioids.

- These substances are opiates and appear to have no legitimate therapeutic use.
- The opioid analgesic substance 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methylbenzamide (**AH-7921**), a structural isomer of U-47700, is already included in Schedule 9.

### ***Australian regulatory information***

U-47700 does not have legitimate medical use in Australia and is not in any registered medicines. No legitimate industrial uses have been identified.

AH-7921 does not have legitimate medical use in Australia.

NICNAS could not locate any AICS-listed chemicals meeting this description. The National Chemical Inventories program includes one chemical, 116174-38-0 (benzamide, *N* (cyanomethyl)-*N*-[(1*R*,2*R*)-2-[[[(methylsulfonyl)oxy]methyl]cyclohexyl]-), with presumed industrial use, but this was not considered to fall within the relevant class description *N* (alkylamino)cyclohexylbenzamides. This has been pre-registered under REACH, but it is not on any chemicals inventory.

### ***International regulations***

The US DEA and FDA in 2016 placed U-47700 and its isomers, esters, ethers, salts and salts of isomers, esters and ethers, in Schedule 1, effective from 14 November 2016, following confirmed deaths and inclusion of the powder form in counterfeit pharmaceuticals.

In the U.K. U-47700 is controlled under the Psychoactive Substances Act 2016. In Sweden, following sale in 2016 as a designer drug, U-47700 was made illegal in January 2016. Finland labelled U-47700 a controlled substance in September 2015.

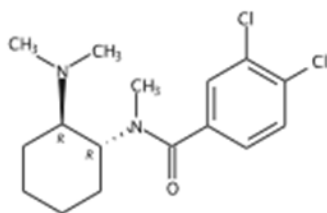
U-47700 was reviewed at the World Health Organization (WHO) Expert Committee on Drug Dependence summit in November 2016.

U-47700 is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

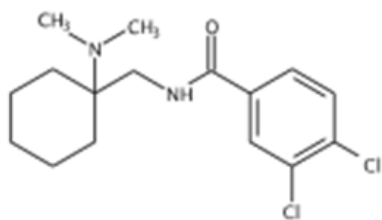
No information is available on related scheduling in New Zealand.

### ***Substance summary***

*N*-(alkylamino)cyclohexylbenzamides are synthetic opioid analgesics, and include 3,4-dichloro-*N*-[(1*R*,2*R*)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide, U-47700, which is unscheduled, and 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide, AH-7921, which has been in Schedule 9 since 2014. U-47700 is a structural isomer of AH-7921. In both isomers, the benzamide moiety is dichlorinated at the 3 and 4 ring positions and the aminocyclohexane moiety is *N,N*-dimethylated.



**Figure 2.1: Chemical structure of U-47700 (free base, trans stereochemistry)**



**Figure 2.2: Chemical structure of AH-7921 (free base, trans stereochemistry)**

**Table 2.1: General information**

Property	U-47700	AH-7921
CAS No.	82657-23-6 (free base, trans); 121348-98-9 (form not specified)	55154-30-8 (free base); 41804-96-0 (hydrochloride salt)
IUPAC name	3,4-dichloro- <i>N</i> -[(1 <i>R</i> ,2 <i>R</i> )-2-(dimethylamino)cyclohexyl]- <i>N</i> -methylbenzamide	3,4-dichloro- <i>N</i> -{[1-(dimethylamino)cyclohexyl]methyl}benzamide
Synonyms	U4, fake morphine, pinky, pink <sup>33</sup>	1-(3,4-dichlorobenzamidomethyl)cyclohexyldimethylamine; doxylam
Molecular formula	C <sub>16</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O	C <sub>16</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O
Molecular weight	329.3 g/mol	329.3 g/mol
Scheduling status	Unscheduled	Schedule 9

#### U-47700

U-47700 is a white powder. Chemical properties of U-47700 include: melting point: 97–98.5°C, boiling point 465°C, solubility is sparingly soluble in water (0.49 g/L), at pH 10.36 very soluble (527 g/L). U-47700 contains 2 chiral centres at the bonds to the 2 nitrogens off the ring resulting in 4 isomers; *cis* and *trans* each have 2 enantiomers [*cis*: are (1*R*,2*R*), and (1*S*,2*S*); *trans* are (1*R*,2*S*) and (1*S*,2*R*)]. The absolute configuration of the  $\mu$ -agonist enantiomer was originally reported as *R,R*.

Identified risks of U-47700 include developing substance abuse, overdose, and death similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc). Since 2015, abuse of U-47700 has been reported as the single substance and in combination with other substances, including heroin, fentanyl, and furanyl fentanyl. The population likely to abuse U-47700 appears to overlap with the populations abusing prescription opioid analgesics, other “designer opioids,” and heroin, as evidenced by drug use history documented in U-47700 fatal overdose cases.

U-47700 became the lead compound of several selective kappa-opioid receptor ligands such as U-50488, U-51754 (with a single methylene spacer difference) and U-69,593, with similar structures<sup>34</sup>. It has no medical use<sup>35</sup>. Research use has been reported<sup>36</sup>.

<sup>33</sup> [U-47700: Everything You Need to Know About Deadly New Drug](#)

Media reports that U-47700 can be taken by injection, inhalation, and oral administration. An internet search indicates that U-47700 is available via the internet for up to \$US35/gram.

The DEA placement of U-47700 in Schedule 1 raises concerns that, since this is obtained through illicit sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user.

The DEA placement of U-47700 in Schedule 1 states:

- Evidence suggests that the pattern of abuse of U-47700 parallels that of heroin, prescription opioid analgesics, and other novel opioids. Seizures of U-47700 have been encountered in powder form and in counterfeit tablets that mimic pharmaceutical opioids.
- U-47700 is available over the Internet and is marketed as a “research chemical.”
- U-47700 exhibits pharmacological profiles similar to that of morphine and other  $\mu$ -opioid receptor agonists. Cases of intoxication are reported in the literature with morbidity and mortality associated with U-47700 use. The toxic effects of U-47700 in humans are demonstrated by overdoses and overdose fatalities associated with this substance, as reported in the scientific literature.

Adverse reactions reported in humans are described in the WHO UNODC report. This report details misuse, abuse and dependence by humans and indicates significant abuse potential and that there are no marketing authorizations as a medicinal product for U-47700 and it has no legitimate industrial use. Seizures have been reported relating to use in Europe and the USA with reports of opiate-like adverse effects and associated fatalities.

#### AH-7921

AH-7921 is an opioid analgesic substance selective for the  $\mu$ -opioid receptor, having around 80% the potency of morphine when administered orally. It was discovered in the 1970's by a team at Allan and Hanburys Ltd, a British pharmaceutical manufacturer. A trivial name, doxylam, has been proposed for this compound, but it has never been sold commercially for medical use. In 2013, AH-7921 was discovered to have been used as an active ingredient in "synthetic cannabis" products in Japan.

The free base form of AH-7921 is a solid; its melting point is not known. The hydrochloride salt, also a solid, has been documented to have a melting point of 215-216°C. This refers to a 1974 study by Harper *et al.*, which details that the LD<sub>50</sub> of AH-7921 is higher than 10 mg/kg upon intravenous administration in the rat. No studies were identified examining toxicity in humans and insufficient information was available to determine its acute toxicity.

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<sup>34</sup> Loew, G.; Lawson, J.; Toll, L.; Frenking, G.; Berzetei-Gurske, I.; Polgar, W. (1988). ["Structure activity studies of two classes of  \$\beta\$ -amino-amides: the search for kappa-selective opioids"](#) (PDF). *NIDA Research Monograph*. **90**: 144–151. [ISSN 1046-9516](#). [PMID 2855852](#)

Szmuszkovicz, Jacob; Zhao, Shikai; Totleben, Michael J.; Mizesak, Stephen A.; Freeman, Jeremiah P. ["Phenanthridone Analogs of the Opiate Agonist U-47,700 in the trans-1,2-Diaminocyclohexane Benzamide Series"](#). *Heterocycles*. **52** (1): 325–332. [doi:10.3987/com-99-s27](#).

<sup>35</sup> [U-47700 Critical Review Report Agenda Item 4.1](#)

<sup>36</sup> Szmuszkovicz, Jacob (1999). ["U-50,488 and the  \$\kappa\$  receptor: A personalized account covering the period 1973 to 1990"](#). *Progress in Drug Research*. Progress in Drug Research. Birkhäuser Basel. pp. 167–195. [doi:10.1007/978-3-0348-8730-4\\_4](#). [ISBN 9783034887304](#)

Tsibulnikov, S. Yu; Maslov, L. N.; Mukhomedzyanov, A. V.; Krylatov, A. V.; Tsibulnikova, M. R.; Lishmanov, Yu B. (October 2015). ["Prospects of Using of  \$\kappa\$ -Opioid Receptor Agonists U-50,488 and ICI 199,441 for Improving Heart Resistance to Ischemia/Reperfusion"](#). *Bulletin of Experimental Biology and Medicine*. **159** (6): 718–721. [doi:10.1007/s10517-015-3057-8](#). [ISSN 1573-8221](#). [PMID 26519268](#)



### ***Pre-meeting public submissions***

One (1) submission was received. The submission indicated that there were no known non-medical uses of the substances. Further information may be required to assess the impact of the regulation proposal.

The [public submission](#) will be made available on the TGA website.

### ***Summary of ACCS-ACMS advice to the delegate***

The committee advised that a new Schedule 9 entry be created for N-(alkylamino)cyclohexylbenzamides.

#### **Schedule 9 – Proposed New Entries**

**N-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES except** when separately specified in these Schedules.

**N-(ALKYLAMINO)CYCLOHEXYLMETHYLENEBENZAMIDES except** when separately specified in these Schedules.

**3,4-DICHLORO-N-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-N-METHYLBENZAMIDE (U-47700).**

#### **Index – Proposed New Entries**

##### **N-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES**

cross reference: 3,4-DICHLORO-N-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-N-METHYLBENZAMIDE \*(U-47700)

Schedule 9

##### **N-(ALKYLAMINO)CYCLOHEXYLMETHYLENEBENZAMIDES except when separately specified in these Schedules.**

Cross reference: 3,4-DICHLORO-N-[[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL]BENZAMIDE \*(AH-7921)

Schedule 9

##### **3,4-DICHLORO-N-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-N-METHYLBENZAMIDE (U-47700)**

cross reference: N-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES

Schedule 9

The committee also recommended an implementation date of **1 October 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- There is a significant public health risk similar to other opioid analgesics, such as morphine and fentanyl, including abuse potential, dependence, toxicity and overdose. Furthermore, N-(alkylamino)cyclohexylbenzamides poses a risk of overdose.
- There are no registered products, and there are no benefits from therapeutic use for N-(alkylamino)cyclohexylbenzamides.

- Toxicity reports for *N*-(alkylamino)cyclohexylbenzamides are similar to other opioid analgesics such as fentanyl and morphine, which includes fatal overdose cases. There is also a significant potential for abuse similar to heroin and other illicit prescription and novel opioids.
- There have been reports of illicit use. *N*-(alkylamino)cyclohexylbenzamides are also likely to have significant abuse liability given pharmacological profile. Although no animal studies are available to confirm this, the WHO report describes 'user reports' of tolerance and craving.
- Since *N*-(alkylamino)cyclohexylbenzamides are obtained through illicit sources, the identity, purity, and quantity are uncertain, are inconsistent and therefore pose significant risks to the end-user.
- There are no known medical or industrial uses.
- Significant mortality has been noted internationally. They may be sold as heroin, or mixed with heroin, and this contributes to overdoses.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to create new Schedule 9 entries for *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides. The proposed Schedule entry is as follows:

#### **Schedule 9 – New Entries**

*N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES **except** when separately specified in these Schedules.

*N,N*-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES **except** when separately specified in these Schedules.

3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700).

#### **Index – Proposed New Entries**

##### ***N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES**

cross reference: 3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE \*(U-47700)

Schedule 9

## ***N,N*-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES**

Cross reference: 3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL}BENZAMIDE \*(AH-7921)

Schedule 9

## **3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700)**

cross reference: *N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES

Schedule 9

The proposed implementation date is **1 October 2017**, as this is the earliest possible implementation date.

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 a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision comprised the following:

- Independent expert advice regarding the appropriate naming of the group entries was received and is reflected in the proposed wording of the schedule entries.
- The delegate acknowledges and agrees with the committee's advice:
  - There is a significant public health risk similar to other opioid analgesics, such as morphine and fentanyl, including abuse potential, dependence, toxicity and overdose. Furthermore, *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides pose a risk of overdose.
  - There are no registered products, and there are no benefits from therapeutic use for *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides.
  - Toxicity reports for *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides are similar to other opioid analgesics such as fentanyl and morphine, which includes fatal overdose cases. There is also a significant potential for abuse similar to heroin and other illicit prescription and novel opioids.
  - There have been reports of illicit use. *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides are also likely to have significant abuse liability given pharmacological profile. Although no animal studies are available to confirm this, the WHO report describes 'user reports' of tolerance and craving.
  - Since *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides are obtained through illicit sources, the identity, purity, and quantity are uncertain, are inconsistent and therefore pose significant risks to the end-user.
  - There are no known medical or industrial uses.
  - Significant mortality has been noted internationally. They may be sold as heroin, or mixed with heroin, and this contributes to overdoses.

### ***Public submissions on the interim decision***

No submissions were received.

### ***Delegate's final decision***

As no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to create new Schedule 9 entries for *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides. The implementation date is **1 October 2017**.

## **1.8. In Vitro Diagnostic and Analytical Preparations**

### ***Referred scheduling proposal***

An application was submitted for consideration by the delegate to seek advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on a proposal to amend 'Part 5, Appendix A General Exemptions of the Poisons Standard' to include Schedule 9 poisons at 0.001 per cent or less as exemptions for in vitro diagnostic and analytical preparations.

### ***Current scheduling status***

In Australia, poisons in Schedules 1 to 8 at concentrations of up to 0.001 per cent in in vitro diagnostic and analytical preparations are included in Appendix A as follows:

#### **Appendix A – General Exemptions**

IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to 8.

### ***Scheduling history***

In 1987, the Drugs and Poisons Scheduling Committee (DPSC) rejected a proposal that a general exemption for all scheduled substances when incorporated into an in vitro diagnostic test kit be included in the Poisons standard. The committee felt that each case needs to be considered on its merits so that substances contained in these kits can be properly assessed and the correct labelling, storage and clinical advice given.

### ***Scheduling application***

This is a general application. The applicant's proposed amendment to the Poisons Standard is as follows:

#### **Appendix A – Amend Entry**

IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to ~~8~~<sup>9</sup>

The applicant's reasons for the request are:

- This amendment is requested to allow in vitro diagnostic medical device (IVD) companies to legally import, store and supply IVDs containing very small amounts of substances included in Schedule 9.
- These IVDs items are positive controls used for screening clinical specimens for the detection of drugs of abuse. The amount of drugs included in the controls is very small ( $\leq 300$  ng/mL) well below the amount specified in the standard. The range of drugs which are screened for varies but the most common drugs are MDMA, LSD, phencyclidine (PCP) and methaqualone.

## ***Australian regulatory information***

In Australia, all in vitro diagnostic medical devices (IVD medical devices or IVDs) that are intended to be used for a therapeutic purpose are subject to regulation under the *Therapeutic Goods Act 1989*. A new regulatory framework for IVDs was implemented on 1 July 2010, following amendments made to the *Therapeutic Goods (Medical Devices) Regulations 2002* (the Regulations) to include IVDs as a subset of medical devices.

The changes made to the legislation apply to all IVDs, and require that all manufacturers of IVDs certify that their products are safe, perform appropriately for their intended purpose, and are manufactured to a high standard of quality by complying with a set of Essential Principles (EPs) to identify performance levels required, hazards to be addressed, or issues to be considered. The EPs for safety and performance form the basis of the IVD regulatory framework and are set out in Schedule 1 of the Regulations.

In vitro diagnostic medical devices (IVDs) are defined as:

- a) a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with another diagnostic product for in vitro use; and
- b) intended by the manufacturer to be used in vitro for the examination of a specimen derived from the human body, solely or principally for:
  - i) giving information about a physiological or pathological state or a congenital abnormality; or
  - ii) determining safety and compatibility with a potential recipient; or
  - iii) monitoring therapeutic measures; and
- c) not a product that is:
  - i) intended for general laboratory use; and
  - ii) not manufactured, sold or presented for use as an IVD medical device.

## ***International regulations***

### ***New Zealand***

In New Zealand, IVDs are currently exempt from mandatory notification to WAND (web assisted notification of devices) database but must still comply with the requirements of the Medicines Act 1981 and its Regulations.<sup>37</sup>

### ***USA***

An overview of IVD Regulation is available on the FDA website.<sup>38</sup>

- [21 CFR 864.4010\(a\)](#) is applied to general purpose reagents (GPRs). A GPR is a chemical reagent that has general laboratory application, is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and is not labelled or otherwise intended for a specific diagnostic application. GPRs do not include laboratory machinery, automated or powered systems).

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<sup>37</sup> NZ: [Medical Devices: In-Vitro Diagnostic \(IVD\) Devices](#)

<sup>38</sup> USA, IVD Regulation: [Overview of IVD Regulation](#)

- [21 CFR 864.4020\(a\)](#) is used to classify analyte specific reagents (ASRs). ASRs are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens) used in IVDs.

Also on the FDA website is a review on Drugs of Abuse Tests.<sup>39</sup>

### Canada

In Canada,<sup>40</sup> reagents, instruments, apparatus, equipment or systems not manufactured, sold or represented by manufacturers for use in *in vitro* diagnostic applications are not considered to be *in vitro* diagnostic devices (IVDDs). This includes products used in general laboratory applications, even if they are used by laboratories to develop their own diagnostic assays for the laboratory's own use.

IVDDs labelled "For Research Use Only" (not otherwise labelled or otherwise represented by a manufacturer for a specific diagnostic application, or labelled with specific performance characteristics, or a bibliography listing articles referring to the use of the marker for a specific application) are exempt from the *Medical Devices Regulations*.

In accordance with subparagraph 3(2) of the Regulations, all *in vitro* diagnostic products that are a drug or contain a drug listed in Schedule E or F to the *Food and Drugs Act*, in the Schedule to Part G or Part J of the *Food and Drug Regulations*, in the Schedules to the *Controlled Drugs and Substances Act*, or in the Schedule to the *Narcotic Control Regulations*, are not subject to the *Medical Devices Regulations*. The following is a short description of these schedules.

Section 15 of the *Act* prohibits the sale of a drug mentioned in Schedule F. Therefore, if an *in vitro* diagnostic product was a drug or contained a drug listed on Schedule F to the *Act*, its sale would be prohibited. In the case of *in vitro* diagnostic products that was a drug or contained a drug listed on Schedule E to the *Act*, it would be subject to the provisions of the *Food and Drug Regulations*.

*In vitro* diagnostic products listed on the Schedule to Part G or the Schedule to Part J of the *Food and Drug Regulations* are subject to the provisions of the *Controlled Drugs and Substances Act* (CDSA) and the *Food and Drug Regulations*. The Schedule to Part G lists controlled drugs, such as barbiturates and anabolic steroids. The Schedule to Part J lists restricted drugs, such as some amphetamines and lysergic acid diethylamide. All drugs listed in Schedules G and J of the *F&D Regulations* are also listed on the Schedules to the CDSA.

In addition to the products listed on Schedules G and J of the *Food and Drug Regulations* and on the Schedule to the *Narcotic Controlled Regulations*, there are other products listed on the schedules to the CDSA that are also not subject to the *Medical Devices Regulations*.

*In vitro* diagnostic products listed on the Schedule to the *Narcotic Controlled Regulations* are subject to the provisions of the CDSA (also listed in its schedules) and of the *Narcotic Controlled Regulations*.

### Europe

There is guidance document regarding IVD and medical devices in the EU.<sup>41</sup> In the EU, devices intended to be used only in the course of law enforcement or other non-medical purposes, for example paternity tests or tests for detecting drugs of abuse/alcohol, are not IVD's. If however, the *in vitro* examination of human specimens with a medical purpose is one of the intended uses of a specific product, the IVD Directive will apply.<sup>42</sup> A list of substances used in IVDs in the EU is given in the IDV

<sup>39</sup> USA, review on [Drugs of Abuse Tests](#)

<sup>40</sup> Canada: [Guidance Document: Guidance for the Risk-based Classification System for In Vitro Diagnostic Devices \(IVDDs\)](#)

<sup>41</sup> EU, IVD medical devices review: [MEDDEV. 2.14/1 rev. 1 Guidelines on Medical Devices: IVD Guidances: Borderline issues - A Guide for Manufacturers and Notified Bodies \(pdf.94kb\)](#)

<sup>42</sup> IVD directive: [In Vitro Diagnostic Product Classification - Revision 5 \(pdf.141kb\)](#)

directive and includes Drugs of Abuse/Toxicology such as amphetamines, barbiturates, benzodiazepines, cannabinoids THC, cocaine, codeine, morphine's and other.<sup>42</sup>

Examples of test kits are available at the following websites:

- [ThermoFisher Scientific – CEDIA Cocaine OFT Assay](#)
- [Agilent – LSD Analysis in Urine by LC-MS](#)
- [Roche – LSD Assay](#)

### ***Substance summary***

An in vitro diagnostic medical device (IVD):

- is any medical device which is a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination (with other diagnostic goods for in vitro use); and
- intended by the manufacturer to be used in vitro for the examination of specimens derived from the human body, solely or principally for the purpose of giving information about a physiological or pathological state, a congenital abnormality or to determine safety and compatibility with a potential recipient or to monitor therapeutic measures.

The range of drugs tested varies but currently the most common are MDMA, LSD, phencyclidine (PCP) and methaqualone. In vitro diagnostic preparations for the screening of drugs of abuse are not therapeutic goods and therefore do not require approval by the TGA. However, the controls and calibrators for the IVDs are therapeutic goods and do require TGA approval. Therefore, the products related to this application are all evaluated and approved by the TGA before supply.

The products involved are controls or calibrators, i.e. urine or serum samples, that contain specified amounts of a range of commonly used drugs of abuse. The products are used exclusively in pathology laboratories, which are secure premises from which diversion is unlikely. Also the amount of drug present in the products is very small ( $\leq 300$  ng /mL) and therefore the risk of diversion or abuse is considered to be low.

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACCS-ACMS advice to the delegate***

On the basis of the information contained in the application, the committee recommended that the current inclusion in Appendix A (General Exemptions) of 'IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to 8' remains appropriate.

The committee suggested that additional information may be available regarding the scope of use from IVD Australia, MTAA and workplace testing facilities, and requested the Secretariat to engage with these bodies to gain further information to support reconsideration by the committee/delegate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- Consideration of Schedule 9 substances proposed for inclusion in Appendix A should be considered on a case-by-case basis.



- Some Schedule 9 poisons are very potent and the potential diversion of small amounts of specific chemicals may be problematic.
- The toxicity of the Schedule 9 poisons varies according to the class of substance (opioid, hallucinogen, stimulant) and is dose related. Schedule 9 poisons can lead to serious health risks if diverted due to their toxicity and potency.
- The committee noted the risk of diversion from an IVD is low from authorised diagnostic laboratories however external to these, the risks outweighed the benefit.
- The potential for abuse of *in vitro* diagnostic substances would be significantly increased when provided in analytical solutions, however is likely to be very minimal if limited to the well-plate of IVD kits when supplied to NATA accredited laboratories and hospitals, and given the very small quantities (less than or equal to 500 nanograms per mL) in test kits regulated under the Therapeutic Goods (Medical Devices) Regulations 2002, and the matrix in which the Schedule 9 poisons exist (i.e. urine).
- There is a growing area of workplace testing, as well as testing that is undertaken in laboratories and universities, and limiting supply to forensic laboratories, hospitals and workplaces is an important consideration.
- An exemption under Appendix A for Schedule 9 poisons at a concentration of 0.001 per cent or less for in vitro diagnostic and analytical preparations may not automatically apply in all jurisdictions.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision was that the scheduling of IVDs remained appropriate.

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 a substance; (b) the purposes for which a substance is to be used 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 of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision comprised the following:

- The delegate acknowledges the committee's advice.
- Consideration of Schedule 9 substances proposed for inclusion in Appendix A should be considered on a case-by-case basis.
- Some Schedule 9 poisons are very potent and the potential diversion of small amounts of specific chemicals may be problematic.
- The toxicity of the Schedule 9 poisons varies according to the class of substance (opioid, hallucinogen, stimulant) and is dose related. Schedule 9 poisons can lead to serious health risks if diverted due to their toxicity and potency.



- The committee noted the risk of diversion from an IVD is low from authorised diagnostic laboratories however external to these, the risks outweighed the benefit.
- The potential for abuse of in vitro diagnostic substances would be significantly increased when provided in analytical solutions, however is likely to be very minimal if limited to the well-plate of IVD kits when supplied to NATA accredited laboratories and hospitals, and given the very small quantities (less than or equal to 500 nanograms per mL) in test kits regulated under the Therapeutic Goods (Medical Devices) Regulations 2002, and the matrix in which the Schedule 9 poisons exist (i.e. urine).
- There is a growing area of workplace testing, as well as testing that is undertaken in laboratories and universities, and limiting supply to forensic laboratories, hospitals and workplaces is an important consideration.
- An exemption under Appendix A for Schedule 9 poisons at a concentration of 0.001 per cent or less for *in vitro* diagnostic and analytical preparations may not automatically apply in all jurisdictions.
- The current entry remains appropriate, but further information may be available, and will be sought from the applicant, IVD Australia, MTAA and workplace testing facilities to assist reconsideration by the committee/delegate.

### ***Public submissions on the interim decision***

One (1) submission was received which opposed the delegate's interim decision. The main points were:

- It is not viable for many commercial suppliers to import and supply IVD controls and calibrators for Schedule 9 substances under current arrangements. This leads to fewer test brands being available and at higher cost to the laboratories that use them.
- Particular diagnostic tests for Schedule 9 substances may not be available. This is a risk for synthetic cannabinomimetics where there may only be a transient demand for testing for a particular compound.
- It is acknowledged that some Schedule 9 poisons are extremely potent and must be handled appropriately. However, the combination of use in the laboratory and the fact IVD solutions are supplied in very low concentrations and volumes relative to the potency of the product mean that the risk of diversion is low.
- Proposals for individual Schedule 9 substances are always possible but the resources required to prepare an effective submission and the relatively low commercial returns from an individual assay means that this will generally not be a practical pathway.

### ***Delegate's final decision***

The delegate acknowledges that there is strong interest in certain poisons currently in Schedule 9 being available in an IVD test kit. However a general exemption for all Schedule 9 poisons cannot be justified based on the provided information.

A limited exemption may be considered in the future, dependant on which Schedule 9 substances are included in the application. Further information about the presentation of IVD test kits and how the presentation limits diversion should be provided.

In view of this the Scheduling Secretariat will undertake further consultation with the States and Territories, workplace testing groups and IVD manufacturers/peak bodies to work on whether there is potentially a more appropriate scheduling outcome for IVDs that might require access to Schedule 9 substances.

The delegate notes the submission; however, as no new evidence has been received to alter the interim decision the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is that the current inclusion in Appendix A (General Exemptions) of 'IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to 8' remains appropriate.

## 1.9. Sodium $\alpha$ -olefin sulfonates

### *Referred scheduling proposal*

An application was submitted for consideration by the delegate to seek advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on an application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a Schedule 6 entry for sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate.

### *Current scheduling status and relevant scheduling history*

Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are not specifically scheduled and have not been previously considered for scheduling.

However, lauryl sulfate salts are similar surfactants listed in Schedule 6 and Appendix E, Part 2, as follows:

#### **Schedule 6**

LAURYL SULFATE SALTS (excluding their derivatives) **except:**

- a) in wash-off preparations containing 30 per cent or less of lauryl sulfates and, if containing more than 5 per cent of lauryl sulfates, when labelled with a warning to the following effect:  
  
IF IN EYES WASH OUT IMMEDIATELY WITH WATER;
- b) in leave-on preparations containing 1.5 per cent or less of lauryl sulfates;
- c) in toothpaste and oral hygiene preparations containing 5 per cent or less of lauryl sulfates;
- d) in other preparations for animal use containing 2 per cent or less of lauryl sulfates; or
- e) in other preparations containing 30 per cent or less of lauryl sulfates and, if containing more than 5 per cent of lauryl sulfates, when labelled with warnings to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING AND FLUSH SKIN AND HAIR WITH RUNNING WATER.

#### **Appendix E, Part 2:**

LAURYL SULFATE SALTS	
· leave-on or wash-off preparations above 5 per cent.	E1 [If in eyes wash out immediately with water].
· other preparations above 5 per cent.	E1 (as above) and S1 [If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water].

### ***Scheduling application***

This was a general application.

In July 2016, NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) program, submitted a proposal to create new entries for sodium  $\alpha$ -olefin sulfonate (sodium AOS) and sodium alkyl sulfate (sodium AS) in Schedule 6, paralleling that for lauryl sulfates, in order to restrict their use in cosmetic and domestic products. Exemption to scheduling might be applicable at low concentrations.

The applicant's reasons for the request are:

- Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate have reported uses in a range of cosmetic and domestic products in Australia;
- Reported use of sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate in cosmetic and domestic products overseas, potentially available for use in Australia, at concentrations up to 16.5%;
- Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are potential moderate to strong skin irritants at 10% concentration;
- Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are severe eye irritants at concentrations  $\geq 30\%$ ; and
- Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate present similar issues as other surfactants already scheduled in the SUSMP, including sodium lauryl sulfate (SLS).
- There is potential for dermal and ocular exposure to occur at irritating concentrations based on its use pattern. This can be mitigated by labelling and concentration controls. Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are among a large number of surfactants used in Australia that are toxicologically similar to SLS, and these have been identified to be used in comparatively high concentrations.

### ***Australian regulatory information***

Sodium  $\alpha$ -olefin sulfonate (as SODIUM C14-16 OLEFIN SULFONATE) is in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#) as an excipient only for use in topical medicines for dermal application.

Sodium C14-16 olefin sulfonate is in 3 registered products on the ARTG. It is allowed to be used as an excipient in biologicals, devices, export-only, listed medicines, OTC and prescription medicines; and as an active ingredient in biologicals and prescription medicines. Sodium  $\alpha$ -olefin sulfonate is a declarable excipient (i.e. it is required to be declared on the label of a medicine) in accordance with Therapeutic Goods Orders 69, 91 and 92. When used in biologicals, sodium  $\alpha$ -olefin sulfonate can be displayed as a starting material.

Sodium alkyl sulfate is not on the ARTG or on the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#).

### ***International regulations***

#### ***New Zealand***

Sodium  $\alpha$ -olefin sulfonate is included in one cosmetic product in New Zealand as an excipient.

#### ***Canada***

Sodium  $\alpha$ -olefin sulfonate (as sodium C14-16 olefin sulfonate) is listed as a surfactant – cleansing agent for topical use. Further, sodium  $\alpha$ -olefin sulfonates (of chain lengths C12-14, C14-16, C14-18 and C16-18) are considered to be safe when used in rinse-off products and safe up to 2% in leave-on

products. The concentration of the gamma sultone impurity of any formulation (leave-on or rinse-off) is limited to unsubstituted alkane sultones 10 ppm; chlorosultones 1 ppm; and unsaturated sultones 0.1 ppm. Sodium alkyl sulfate (as sodium C12-15 alkyl sulfate) is listed as a non-medical ingredient.

### Substance summary

**Table 2.3A: General information**

Property	Sulfonic acids, C14-16-alkane hydroxyl and C14-16-alkene, sodium salts	Sulfuric acid, mono-C12-18-alkyl esters, sodium salts
CAS name	sodium C14-16-olefin sulfonate	sulfuric acid, mono-C12-18-alkyl (even numbered) esters, sodium salts
CAS number	68439-57-6	68955-19-1
IUPAC and/or common and/or other names	sodium $\alpha$ -olefin sulfonate; sodium AOS (INCI)	sodium alkyl sulfate; sodium AS (INCI)

The following information has been extracted from the [NICNAS IMAP Human Health Tier II group assessment report for sodium  \$\alpha\$ -olefin sulfonate and sodium alkyl sulfate](#).

**Table 2.3B: Acute toxicity end-points for sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate**

Toxicity	Species	Sodium $\alpha$ -olefin sulfonate and sodium alkyl sulfate	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000	Schedule 5
	Mice	1400->2000	
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rabbit	>2000	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	Low	-
Skin irritation	Rabbit	Moderate to severe skin irritants	Schedule 6
Eye irritation	Rabbit	Severe eye irritants	Schedule 6

### Skin Irritation

Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are considered skin irritants:

- In a skin irritation study conducted on six New Zealand White (NZW) rabbits, 0.5 mL of sodium AOS solution (38% active) was applied dermally to shaved, intact and abraded skin for 24 hours under occlusion. The treated site was not washed after the test substance was removed. Very slight irritation was observed on intact skin in 5/6 animals. One of the six animals had well-defined erythema, which had completely reversed by 72 hours after dosing. Five of the six animals showed well-defined erythema on the abraded skin at 24 hours after dosing. Very slight erythema in all animals and oedema in 2/6 animals were reported, which persisted after 72 hours post dosing on abraded skin (REACH).

- In another skin irritation study conducted in six NZW rabbits, 0.5 mL of sodium AOS solution (38% active) was applied dermally to shaved, intact and abraded skin for four hours under semi-occlusion. The applied site was washed to remove the test substance. All six animals showed moderate to severe reactions with eschar formation, one with cracking at the treatment site at 72 hours after dosing. The reactions were slightly worse in abraded skin than intact skin (REACH).
- In an irritation study conducted according to OECD Test Guideline (TG) 404, 0.5 g of sodium AS powder (88.7% purity) was applied dermally (semi-occlusive) to three New Zealand White rabbits for four hours. Erythema and moderate oedema were observed up to seven days after the patches were removed. All signs of irritation were completely resolved 14 days after dosing (REACH).
- Skin irritation (erythema and oedema) was also reported following a four-hour application of 5–25% sodium lauryl sulfate (SLS) solution on intact rabbit skin (NICNAS).

#### *Eye irritation*

Based on the data available, sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are considered severe eye irritants:

- In an eye irritation study conducted according to OECD TG 405, 0.1 mL of sodium AOS (30% active) was applied to eyes of three NZW rabbits and observed for 21 days. Observed effects included slight corneal redness, slight iritis and conjunctival effects (erythema, swelling and chemosis). Except for chemosis, all eye irritation effects persisted for up to 21 days (REACH).
- In another eye irritation study conducted in six NZW rabbits, 0.1 mL of sodium AOS (38% active) was applied to the eyes with or without washing. Observation times were 24, 48 and 72 hours after administration. Eye irritation effects, which persisted for up to 72 hours, were reported (REACH; HERA 2002).
- The eyes of three NZW rabbits were treated with concentrated (0.08 mL of 90% solution) sodium AOS. The test material was washed off and effects were observed at 24, 48 and 72 hours after application. Observed effects included clear to diffused beefy red erythema and severe swelling of the conjunctivae. Circumcorneal injection (enlargement of the ciliary and conjunctival blood vessels), corneal opacity and discharge (colourless, which changed to white viscous discharge) were also reported. The effects persisted for up to 21 days after dosing (REACH).
- Sodium AS administered at 6% resulted in eye irritation in rabbits, which was reversible within 72 hours of dosing (REACH).

The SLS chemical at 25% in an aqueous solution also caused eye irritation in rabbit eyes, which were not reversible within the 21-day observation period (NICNAS).

#### *Observation in humans*

Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are reported to have irritation potential in humans. Data on SLS are provided as read across since SLS has similar physicochemical properties and reactivity to sodium AOS and sodium AS.

- In a dermal irritation study, human cadaver skin was soaked in sodium olefin sulfonates (C10, 12, 14, 16 and 18) for one, three, six and 24 hour and was compared with skin soaked in distilled water for the same period. Maximum swelling was seen for the C12 and C14 olefin sulfonates (REACH).
- In a controlled human exposure, repeated application of 1% alkyl sulfates to the skin of human volunteers did not produce adverse reactions, while concentrations of 10% were regarded as moderate to strong irritants (HERA, 2002).
- Clinical studies in humans reported that SLS caused skin irritation following patch testing at a  $\geq 2\%$  concentration. The irritation increases with increasing concentration and length of contact with the skin (NICNAS).

- SLS has been reported to cause irritation in the respiratory tract and oral mucosa, especially in individuals predisposed to recurrent mouth ulcers (NICNAS).
- It has also been reported that SLS was the most common cause of eye irritation in commercial shampoos (NICNAS).

#### *Sensitisation*

Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are not expected to be skin sensitisers, based on the available information.

#### *Repeat-dose toxicity*

Based on the data available, sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are not expected to cause serious damage to health from repeated oral and dermal exposure. No information was available for repeated dose toxicity by the inhalation route.

#### *Genotoxicity*

Based on the negative results observed in several *in vitro* and *in vivo* genotoxicity studies, sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are not expected to be genotoxic.

#### *Carcinogenicity*

Based on available data, sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are not considered to be carcinogenic.

#### *Reproduction and developmental toxicity*

Based on the limited available data, Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are not expected to have reproductive and developmental toxicity.

#### *Public exposure*

Sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are reported to be used in cosmetic and domestic products in Australia.

Australian and overseas information suggests that sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate are generally used at concentrations up to 16% in cosmetics and at up to 16.5% for domestic purposes (i.e. hand dishwashing liquid) (HERA 2002).

Considering the critical health effects identified for sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate, the highest concern relates to skin and eye irritation. There is the potential for skin contact to occur when using domestic products such as laundry detergents or hand washing liquid. However, such products are intended to be rinsed off from the skin after use. There is also the potential for ocular exposure in a domestic setting.

#### ***Pre-meeting public submissions***

Three (3) public submissions were received. All three submissions opposed the scheduling proposal. The main points were:

- A generic group entry of C12-C18 alkyl length surfactants cannot be supported due to differing characteristics of varying lengths of alkyl chains and would hinder attempts by industry to formulate less irritating surfactants.
- Due to surfactants being used for cleaning the body or domestic surfaces for decades, consumers are already knowledgeable in the appropriate use of surfactants and have a certain use pattern of these products due to this continued use over time.

- Scheduling of all surfactants individually is opposed by most submissions, due to this not aligning with international requirements. These substances are not restricted in cosmetics in the EU and the USA permits their use in rinse-off products at  $\leq 2\%$ .
- Scheduling will not generate a better risk management outcome.
- These surfactants do not require scheduling when used in cosmetic products.
- If scheduling is deemed appropriate, submissions suggested lauryl sulfates scheduling should act as a guide for concentration cut-offs and that a minimum of a 12 month lead-in time be implemented.

The [public submissions](#) are available on the TGA website.

### ***Summary of ACCS-ACMS advice to the delegate***

The committee advised that based on the information contained in the application no scheduling entry could be developed for sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate at this time.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- As surfactants, these substances are widely used domestically, including leave-on and wash-off products and cleaning products.
- There are major public health benefits for infection control within the domestic premises when alkyl sulphonate/sulphate surfactants are available without restriction. Despite their widespread use, there have been minimal adverse events associated with the use of these surfactant substances. However, the data may be inadequate to quantify the public health risks associated with this class of surfactants and that only one chain length tends to be hazardous.
- The chemicals captured by this proposal are very closely related to sodium lauryl sulphate, which has previously been scheduled.
- The toxicity profiles of these substances include potential eye damage at higher concentrations, possible cumulative dermal irritation in leave on applications, and eye irritancy at 30%. The short chain is more potent with strong irritation at lower concentrations compared with long chain. Skin irritation for leave-on products at is  $>2-5\%$  with potency being chain-length dependent. SAS C16-18 appears to show only slight reactions at 31.5%, while C12 showed strong reactions at 25%, but slight at 5%.
- Also considered was the feasibility of industry to implement any scheduling decision without substituting to an unregulated or more toxic substance/s. There may be public health ramifications of substituted surfactants in relation to their purpose, such as cleaning.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989

- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision was that no schedule entry should be created for sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate.

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 a substance; (b) the purposes for which a substance is to be used 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 reasons for the interim decision comprised the following:

- The delegate acknowledges the committee's advice.
- As surfactants, these substances are widely used domestically, including leave-on and wash-off products and cleaning products.
- There are major public health benefits for infection control within the domestic premises when alkyl sulphonate/sulphate surfactants are available without restriction. Despite their widespread use, there have been minimal adverse events associated with the use of these surfactant substances. However the data may be inadequate to quantify the public health risks associated with this class of surfactants and that only one chain length tends to be hazardous.
- The chemicals captured by this proposal are very closely related to sodium lauryl sulphate, which has previously been scheduled.
- The toxicity profiles of these substances include potential eye damage at higher concentrations, possible cumulative dermal irritation in leave on applications, and eye irritancy at 30%. The short chain is more potent with strong irritation at lower concentrations compared with long chain. Skin irritation for leave-on products at is >2-5% with potency being chain-length dependent. SAS C16-18 appears to show only slight reactions at 31.5%, while C12 showed strong reactions at 25%, but slight at 5%.
- Also considered was the feasibility of industry to implement any scheduling decision without substituting to an unregulated or more toxic substance/s. There may be public health ramifications of substituted surfactants in relation to their purpose, such as cleaning.

### ***Public submissions on the interim decision***

One (1) submission was received which supported the interim decision. The main point in support was that the scheduling of individual surfactants is unnecessary due to their well-established history of safe use.

### ***Delegate's final decision***

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

The delegate's final decision is that no scheduling entry be created for sodium  $\alpha$ -olefin sulfonate and sodium alkyl sulfate.



### 3. Advisory Committee on Chemicals Scheduling (ACCS #19)

#### Summary of delegate's final decisions

Substance	Final decision
Ethyl hexanediol	<p><b>Schedule 10 – Delete Entry</b></p> <p><b>Schedule 6 – New Entry</b></p> <p>ETHYL HEXANEDIOL <b>except</b> in preparations containing 5 per cent or less of ethyl hexanediol.</p> <p><b>Schedule 4 – Delete Entry</b></p> <p><b>Appendix E, Part 2 – New Entry</b></p> <p>ETHYL HEXANEDIOL</p> <p>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)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes).</p> <p><b>Appendix F, Part 3 – New Entry</b></p> <p>ETHYL HEXANEDIOL</p> <p>Warning Statements: 79 (will irritate eyes). Safety directions: 1 (avoid contact with eyes).</p> <p><i>The implementation date is <b>1 October 2017</b>.</i></p>
Climbazole	<p><b>Schedule 6 – Amend Entry</b></p> <p>CLIMBAZOLE <b>except</b>:</p> <ul style="list-style-type: none"> <li>a) when included in Schedule 5; or</li> <li>b) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or</li> <li>c) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.</li> </ul> <p><b>Schedule 5 – Amend Entry</b></p> <p>CLIMBAZOLE in preparations containing 40 per cent or less of climbazole <b>except</b>:</p> <ul style="list-style-type: none"> <li>a) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or</li> <li>b) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.</li> </ul>

Substance	Final decision
	<i>The implementation date is 1 June 2018.</i>
m-Aminophenol	<p><b>Schedule 6 – New Entry</b></p> <p><i>m</i>-AMINOPHENOL <b>except</b> when used in hair dye and eyebrow/eyelash preparations at a concentration of 1.2 per cent or less of <i>m</i>-aminophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:</p> <p>KEEP OUT OF REACH OF CHILDREN, and</p> <p>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.</p> <p>written in letters not less than 1.5 mm in height.</p> <p><b>Appendix E, Part 2 – New Entry</b></p> <p><i>m</i>-AMINOPHENOL</p> <p>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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).</p> <p><b>Appendix F, Part 3 – New Entry</b></p> <p><i>m</i>-AMINOPHENOL</p> <p>Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation).</p> <p>Safety directions: 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist).</p> <p><i>The implementation date is 1 June 2018.</i></p>
2-Chloro-6-(ethylamino)-4-nitrophenol	<p><b>Schedule 6 – New Entry</b></p> <p>2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL <b>except:</b></p> <p>a) in non-oxidative hair dye preparations containing 3 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:</p> <p>KEEP OUT OF REACH OF CHILDREN, and</p> <p>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</p> <p>written in letters not less than 1.5 mm in height; or</p> <p>b) in oxidative hair dye preparations containing 1.5 per cent or</p>

Substance	Final decision
	<p>less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:</p> <p>KEEP OUT OF REACH OF CHILDREN, and</p> <p>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</p> <p>written in letters not less than 1.5 mm in height.</p> <p><b>Appendix E, Part 2 – New Entry</b></p> <p>2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL</p> <p>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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).</p> <p><b>Appendix F, Part 3 – New Entry</b></p> <p>2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL</p> <p>Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation).</p> <p>Safety directions: 4 (Avoid contact with skin).</p> <p><i>The implementation date is 1 June 2018.</i></p>
2,4-Diamino-phenoxy-ethanol	<p><b>Schedule 6 – Amend Entry</b></p> <p>2,4-DIAMINOPHENOXYETHANOL <b>except</b> when used in hair dye and eyebrow/eyelash preparations at a concentration of 2 per cent or less of 2,4-diaminophenoxyethanol after mixing for use when the immediate container and primary pack are labelled with the following statements:</p> <p>KEEP OUT OF REACH OF CHILDREN, and</p> <p>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.</p> <p>written in letters not less than 1.5 mm in height.</p> <p><b>Appendix E, Part 2 – Amend Entry</b></p> <p>2,4-DIAMINO-PHENOXYETHANOL</p> <p>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)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to</p>

Substance	Final decision
	<p>stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).</p> <p><b>Appendix F, Part 3 – Amend Entry</b></p> <p>2,4-DIAMINO-PHENOXYETHANOL</p> <p>Warning statement: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).</p> <p>Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).</p> <p><i>The implementation date is <b>1 June 2018</b>.</i></p>
Isoeugenol	<p><b>Schedule 6 – Amend Entry</b></p> <p>ISOEUGENOL <b>except</b>:</p> <ul style="list-style-type: none"> <li>a) when included in Schedule 5; or</li> <li>b) in preparations not intended for skin contact containing 10 per cent or less of isoeugenol; or</li> <li>c) in preparations intended for skin contact containing 0.02 per cent or less of isoeugenol.</li> </ul> <p><b>Schedule 5 – Amend Entry</b></p> <p>ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol <b>except</b> in preparations containing 10 per cent or less of isoeugenol.</p> <p><b>Appendix E, Part 2 – New Entry</b></p> <p>ISOEUGENOL</p> <p>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), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).</p> <p><b>Appendix F, Part 3 – New Entry</b></p> <p>ISOEUGENOL</p> <p>Warning statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).</p> <p>Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).</p>

Substance	Final decision
	<i>The implementation date is <b>1 October 2018</b>.</i>
<i>Aureobasidium pullulans</i> (strains DSM 14940 and DSM 14941)	<b>Appendix B – New Entry</b> AUREOBASIDIUM PULLULANS (Strains DSM14940 and DSM14941) <i>The implementation date is <b>1 October 2017</b>.</i>

### 3.1 Ethyl hexanediol

#### *Referred scheduling proposal*

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to amend the scheduling of ethyl hexanediol by replacing the Schedule 10 entry with a Schedule 6 entry to allow for human use.

#### *Scheduling application*

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

##### **Schedule 10 – Delete Entry**

~~ETHYLHEXANEDIOL for human use.~~

##### **Schedule 6 – New Entry**

**ETHYL HEXANEDIOL.**

##### **Schedule 4 – Current Entry**

ETHYL HEXANEDIOL for animal use.

##### **Appendix E, Part 2**

**ETHYL HEXANEDIOL**

**Standard statement: E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes).**

The applicant's reasons for the request are:

- There are concerns about developmental toxicity for the current Schedule 10 entry for ethyl hexanediol (National Drugs and Poisons Scheduling Committee (NDPSC), 2012); however, publicly available data on reproductive toxicity indicated effects at high doses only and/or concurrent with maternal toxicity;
- The only critical health effect identified and classified was eye irritation;
- There are no international restrictions;
- International sources have determined that ethyl hexanediol is a safe cosmetic ingredient (Cosmetic Ingredient Review (CIR), 2011);
- Cosmetic and/or domestic use is considered to be limited; and

- Structurally similar chemicals, 2-ethylhexanoic acid (and its alkyl esters) and 2-ethylhexanol (and its derivatives), have similar uses but higher potency for critical health effects. 2-Ethylhexanoic acid is in Schedule 6 with a 5% exemption cut-off and 2-ethylhexanol is currently being considered by NICNAS as to whether Schedule 6 with appropriate low-level cut-offs are required.

### ***Current scheduling status and relevant scheduling history***

Ethyl hexanediol is currently listed in Schedules 4 and 10 as follows:

#### **Schedule 10**

ETHYLHEXANEDIOL for human use.

#### **Schedule 4**

ETHYLHEXANEDIOL for animal use.

The structurally similar chemical 2-ethylhexanoic acid is in Schedule 6 and Appendices E and F as follows:

#### **Schedule 6**

2-ETHYLHEXANOIC ACID and its alkyl esters **except** in preparations containing 5 per cent or less calculated as 2-ethylhexanoic acid.

#### **Appendix E, Part 2**

2-ETHYLHEXANOIC ACID

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)).

#### **Appendix F, Part 3**

2-ETHYLHEXANOIC ACID

Warning statements: 53 (CAUTION – (Name of substance) should not be used by pregnant women).

Prior to 1991, ethyl hexanediol was listed in Appendix B of the then SUSDP. In November 1991, the Drugs and Poisons Scheduling Sub-Committee (DPSSC) considered a request from a member to remove ethyl hexanediol from Appendix B in view of reports linking the insect repellent to teratogenic effects. The committee advised deletion from Appendix B, while establishing whether the substance is used in Australia.

From February - May 1993, the DPSSC reviewed the toxicology of ethyl hexanediol following a US EPA cancellation of registrations prohibiting sale, distribution or use of existing stocks of ethyl hexanediol. At its November 1991 meeting, the DPSSC had requested that the Chemicals Safety Unit (CSU) establish whether ethyl hexanediol was used in Australia, and if so request relevant data from sponsors in order to establish a schedule. At that meeting, the DPSSC had advised that ethyl hexanediol be deleted from Appendix B. The committee considered and created a new Appendix C entry for ethyl hexanediol, following concerns about malformations evident in rat studies, which appeared to be dose-related.

In February 2000, the National Drugs and Poisons Schedule Committee (NDPSC) considered an exemption from Appendix C for cosmetic use. The committee did not support exemption of ethyl hexanediol from Appendix C because of unacceptable risk of teratogenicity associated with the use of the substance.

In October 2006, the NDPSC included ethyl hexanediol in Schedule 4 to harmonise with New Zealand. In February 2007 the NDPSC agreed that a Schedule 4 entry for ethyl hexanediol would conflict with the then existing Appendix C (now Schedule 10) entry. The committee agreed that the Schedule 4

entry was only intended to capture animal therapeutic use, and that it remained appropriate for human therapeutic use to be captured by Appendix C. The February 2007 NDPSC Meeting confirmed that the Schedule 4 entry was intended to capture animal therapeutic use only.

The overlap between entries was considered by the NDPSC from June - October 2008. The NDPSC confirmed that the Appendix C entry for ethyl hexanediol captured all human use.

In February 2009, the NDPSC amended the Schedule 4 entry to reflect its use in animal treatment only with the addition 'for animal treatment'.

### ***Australian regulatory information***

Ethyl hexanediol is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017, and a search of the Australian Register of Therapeutic Goods (ARTG) found it is neither an excipient nor active in any listed medicines.

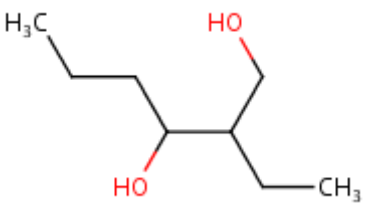
Ethyl hexanediol is not in any currently registered products regulated by the APVMA.

### ***International regulations***

Ethyl hexanediol was listed as a hazardous substance by the EPA in New Zealand in December 2006 (HSNO Approval Code HSR003694).

### ***Substance summary***

**Table 3.1A: Chemical information**

Property	Ethyl hexanediol
CAS name	1,3-hexanediol, 2-ethyl-
CAS number	94-96-2
Chemical structure	
IUPAC and/or common and/or other names	Ethyl hexanediol (INCI); 1,3-hexanediol, 2-ethyl- (CAS); hexanediol; octylene glycol; ethohexadiol (AAN); 2-ethylhexane-1,3-diol (IUPAC)
Molecular formula	C <sub>8</sub> H <sub>18</sub> O <sub>2</sub>
Molecular weight	146.3 g/mol

The following information was extracted from [the NICNAS IMAP Human Health Tier II assessment report for ethyl hexanediol](#).

**Table 3.1B: Acute toxicity end-points for ethyl hexanediol**

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rats (strain not specified)	2710-9210	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rabbits (strain not specified)	8960-18700	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rats (strain not specified)	>3800	Schedule 5
Skin irritation	New Zealand White rabbits Guinea pigs (Strain not specified) Swiss mice	Mildly irritating (neat chemical)	Schedule 5
Eye irritation	New Zealand White rabbits	Irritating	Schedule 6
Skin sensitisation (Mangusson and Kigman maximisation test and Kodak footpad method)	Guinea pigs (strain not specified; Hartley)	No positive reactions	N/A

*Acute toxicity*

Based on the available oral, dermal and inhalation data, ethyl hexanediol has low acute toxicity.

*Skin irritation*

Ethyl hexanediol is reported to slightly irritate skin:

- In an acute dermal irritation/corrosion study conducted according to OECD TG 404 in New Zealand White rabbits (n = 3/sex), 0.5 mL of undiluted ethyl hexanediol was applied occlusively to clipped dorsal trunk skin for a duration of 4 h and animals were observed for 14 days. Five animals were reported to show slight local erythema (redness) and one showed well-defined local oedema (swelling). All the effects were fully reversed within 24–48 h. The study was concluded that ethyl hexanediol was slightly irritating to skin.
- In another study, 0.5 mL of undiluted ethyl hexanediol was applied occlusively to the shaved dorsal skin of guinea pigs (n = 5), nine times over 11 days. Slight erythema (in 2/5 animals) was observed after three applications and slight to moderate erythema (in 3/5 animals) was observed by the end of the study.
- In an acute toxicity study conducted on New Zealand White rabbits (n = 5/sex/group), undiluted ethyl hexanediol was applied once under occlusive patches to the clipped skin of the trunks for 24 h at a dose of 8, 11.3 or 16 mL/kg bw in males and 4, 8 or 16 mL/kg bw in females. The rabbits were observed for 14 days. There were signs of inflammation, redness and swelling at the dosing site. Redness and swelling reversed by day seven, but desquamation (skin peeling) was still evident at the end of the study.
- In a lifetime study in female Swiss mice (n = 50/dose), 0.2 mL of ethyl hexanediol at concentrations of 10, 50 or 100% in acetone was applied to shaved dorsal skin, twice weekly. Minimal local inflammatory changes including moderate dermatitis were observed.



### *Eye irritation*

Based on the available data, ethyl hexanediol is considered to cause serious eye damage:

- In an ocular irritation study conducted in female rabbits (n = 3), 0.1 mL of undiluted ethyl hexanediol was applied into the conjunctival sac of the eyes. Clouding of the cornea, irritation of the iris and reddening and swelling of the conjunctiva were observed within one hour of administration. Effects on the cornea reversed within one week, effects on the conjunctivae reversed after 10 days, while the iris irritation remained after 21 days. Ethyl hexanediol was reported to be moderately irritating, with a Draize score of 35/110. Similar effects were reported in another two studies. No further details are available.
- In an acute eye irritation study (similar to OECD TG 405) conducted in New Zealand White rabbits (n = 6/treatment), ethyl hexanediol was instilled into the conjunctival sac (0.1 mL) in one group and onto the cornea of the eye (0.01 or 0.005 mL) in two other groups. Animals were examined after 1 h, 24 h and 2, 3 and 7–14 days. The animals treated with 0.1 mL developed mild to severe conjunctivitis, mild to severe chemosis and mild to marked discharge. Moderate iris inflammation and moderate corneal injury were observed. Animals that were administered 0.01 or 0.005 mL had moderate to severe conjunctivitis at the 24 h observation. An overall irritation score of 80/110 was reported for the 1 h observation time point, with all effects being fully reversed within seven days.
- In another study conducted using New Zealand White rabbits (n = 6), 0.1 mL of neat ethyl hexanediol was instilled into the conjunctival sac of one eye; the eyes of three rabbits were washed immediately after chemical instillation, whilst the eyes of the other three rabbits remained unwashed. Both groups were observed immediately and after 1, 24, 48 and 72 h and 7 and 14 days after instillation. Fluorescein staining of the eyes was undertaken 24 h after dosing. Moderate to severe erythema and oedema of the conjunctivae and nictitating membranes (inner eyelids); slight erythema and oedema of the eyelids; slight corneal opacity; and discharge were observed in the unwashed eyes at 24 h. Irritation was less severe in the rinsed eyes, with slight to moderate erythema observed in the conjunctivae and nictitating membranes of the eyes at 1 h. Signs of irritation were reduced by seven days, and fully reversed by 14 days.

### *Sensitization*

Based on the available data, ethyl hexanediol is not expected to be a skin sensitiser.

### *Repeat-dose toxicity*

Based on available data ethyl hexanediol is not considered to cause serious health effects from repeated oral (NOAEL of 480 mg/kg bw/day was reported in rats) or dermal exposure (NOAEL of 1884 mg/kg bw/day was determined in rats). No data are available for inhalation repeat-dose toxicity.

### *Genotoxicity*

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

### *Carcinogenicity*

The limited available data do not indicate that ethyl hexanediol is a carcinogen.

### *Reproduction and developmental toxicity*

Ethyl hexanediol shows specific developmental toxicity, but only at high doses.

- In a developmental toxicity study (similar to OECD TG 414) in pregnant SD rats (n = 8/dose), ethyl hexanediol (in corn oil) was administered by gavage at 500, 1000, 2000 or 4000 mg/kg bw/d on GD 6-15. The NOAEL for maternal and developmental toxicity was reported to be 1000 mg/kg bw/d. Mortalities were reported in the dams at 2000 mg/kg bw/d (1/8) and 4000 mg/kg bw/d (7/8). At doses <sup>3</sup>2000 mg/kg bw/d, signs of weakness, respiratory difficulty, dehydration,

sialorrhoea (excess salivation), gait disturbances, nasal discharge, porphyrin tears, diarrhoea, decreased volume of faeces and unkempt coats were observed in the dams. Hypothermia, partially closed eyes and excessive tearing were observed in the high dose group only. Lesions at necropsy showed that ethyl hexanediol had the greatest effect in the stomach and duodenum; there was excess mucous in the caecum and atrophy of the thymus and adipose tissue. In foetuses from the 2000 mg/kg bw/d group, the incidences of malformations significantly increased (rudimentary or filamentous tails, malformation of rear limbs and joints, shortened trunk and umbilical hernia); and there were also increases in the incidence of haematoma (nine foetuses out of four litters). Two foetuses from different litters exposed to ethyl hexanediol at 1000 mg/kg bw/d and one in the 500 mg/kg bw/d group had rudimentary tails.

- In a developmental toxicity study (similar to OECD TG 414) in pregnant SD rats (n = 25 mated females/dose), ethyl hexanediol was dermally applied (occlusively) at 0, 1, 2 or 4 mL/kg bw/day (equivalent to 0, 935, 1870 and 3740 mg/kg bw/d) for 6 h per day on gestation days (GD) 6–15. Animals were euthanised on GD 21. The NOAEL for maternal reproductive toxicity was reported to be >3768 mg/kg bw/d based on no reported variations in the number of pregnancies, foetal body weights or reproductive factors. At the highest dose, terminal maternal body weights were decreased, and absolute liver weights were significantly increased. Mild skin irritation with exfoliation and crusting were observed in a few females at the mid and high doses. The NOAEL for developmental toxicity was reported to be 942 mg/kg bw/d based on a statistically significant but non-dose-dependent increase in the incidences of skeletal malformation (related to reduced ossification) in the foetuses from the mid and high dose groups, and visceral malformation (e.g. unilateral hydronephrosis) in the foetuses from the high dose groups. It was concluded that ethyl hexanediol is a weak developmental toxicant (CIR, 1994; Ballantyne, 2005; REACH). In two developmental toxicity studies (similar to OECD TG 414) in pregnant SD rats (n=8 – 25/dose), ethyl hexanediol was administered by gavage at 500, 1000, 2000 or 4000 mg/kg bw/day or occlusively 6 h/day at 0, 1, 2 or 4 mL/kg bw/day (equivalent to 0, 935, 1870 and 3740 mg/kg bw/day), on gestation days 6-15.

#### *Observation in humans*

##### **Irritation**

Slight irritation was observed in humans:

- Mild skin irritation was seen in humans administered ethyl hexanediol under semi-occlusive and occlusive conditions for 24 h, repeated 15 times over 21 consecutive days;
- Barely perceivable erythema was observed in 1/106 human subjects under occlusive and semi-occlusive conditions when exposed to ethyl hexanediol at 5%;
- Barely perceivable erythema in 2/30 under semi-occlusive and 4/30 under occlusive conditions were observed immediately and 24 h after application of ethyl hexanediol at 100%. One subject had definite erythema after 72 h.

##### **Skin sensitisation**

Ethyl hexanediol was reported to be a weak skin sensitiser following a human repeated insult patch test. Undiluted ethyl hexanediol was applied occlusively for 24 h, three times per week for three weeks. They were challenged with ethyl hexanediol two weeks later, on an untreated area of skin for 24 h and observed after 24-48 h. There were two incidences of definite erythema 48 h after the challenge patch was removed. Further testing, showed that one of these subjects had a definite sensitisation response.

#### *Public exposure*

Ethyl hexanediol is reported to be used in cosmetic and/or domestic products overseas. Cosmetic use is reported to be limited overseas and domestic use is prohibited in Australia (currently listed in Schedule 10 of the SUSMP). The cosmetic use overseas is assumed to be representative of its potential

use in Australia. Existing controls are such that ethyl hexanediol cannot be used in such products in Australia.

### ***Pre-meeting public submissions***

Two (2) public submissions were received. Both submissions supported the scheduling proposal. The main points were:

- Ethyl hexanediol does not require scheduling control when in human use preparations as the only health concern is eye irritancy (developmental toxicity has been shown to no longer be an issue).
- Scheduling of ethyl hexanediol should align with EU regulations for use in cosmetics.
- There should be low concentration cut-offs for cosmetic and domestic use preparations. If an exemption for cosmetic use at 5% is made, then household products not intended for contact with skin should be exempted at a higher cut-off concentration. This is due to the risk of accidental eye contact being less in domestic products than cosmetics.

The [public submissions](#) will be made available on the TGA website.

### ***Summary of ACCS advice to the delegate***

The committee recommends that the current Schedule 10 and 4 entries for ethyl hexanediol be deleted and that a new Schedule 6 entry be created as follows:

#### **Schedule 10 – Delete Entry**

~~ETHYLHEXANEDIOL for human use.~~

#### **Schedule 6 – New Entry**

**ETHYL HEXANEDIOL *except* in preparations containing 5 per cent or less of ethyl hexanediol.**

#### **Schedule 4 – Delete Entry**

~~ETHYL HEXANEDIOL for animal use.~~

The committee recommended Appendix E/F entries be created as follows:

#### **Appendix E, Part 2 – New Entry**

**ETHYL HEXANEDIOL**

**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)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes).**

#### **Appendix F, Part 3 – New Entry**

**ETHYL HEXANEDIOL**

**Warning Statements: 79 (will irritate eyes).**

**Safety directions: 1 (avoid contact with eyes).**

The committee also advised an implementation date of **1 October 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice comprised the following:

- The substance is used as an ingredient in cosmetic and domestic products internationally, and down-scheduling will allow for this use in Australia.
- It is likely to be in imported products or used in Australia for such purposes if re-scheduled.
- Ethyl hexanediol causes serious eye damage and poses a risk to public health if certain controls are not in place.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is that the current Schedule 10 and 4 entries for ethyl hexanediol be deleted and that a new Schedule 6 entry be created. The proposed Schedule entry is as follows:

#### **Schedule 10 – Delete Entry**

#### **Schedule 6 – New Entry**

ETHYL HEXANEDIOL **except** in preparations containing 5 per cent or less of ethyl hexanediol.

#### **Schedule 4 – Delete Entry**

#### **Appendix E, Part 2 – New Entry**

ETHYL HEXANEDIOL

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)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes)

#### **Appendix F, Part 3 – New Entry**

ETHYL HEXANEDIOL

Warning Statements: 79 (will irritate eyes).

Safety directions: 1 (avoid contact with eyes).

The proposed implementation date is **1 October 2017**, as this is the earliest possible implementation date.

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 a substance; (b) the purposes for which a substance is to be used 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 reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- The substance is used as an ingredient in cosmetic and domestic products internationally, and down-scheduling will allow for this use in Australia.
- It is likely to be in imported products or used in Australia for such purposes if re-scheduled.
- Ethyl hexanediol causes serious eye damage and poses a risk to public health if certain controls are not in place.

#### ***Public submissions on the interim decision***

One (1) submission was received that opposed the delegate's interim decision. The main points were:

- Although the maximum concentration of 5% as stated in the interim decision is in alignment with the US CIR recommendation, there are no restrictions on the use of ethyl hexanediol in cosmetics in the EU, NZ or ASEAN;
- The Schedule 6 entry should be limited to cosmetic preparations as ethyl hexanediol is not restricted for use in non-cosmetic products anywhere else in the world;
- The concentration cut-off to exempt from scheduling of 5% is considered too low for products that are not intended for skin contact as accidental eye exposure is unlikely;
- Ethyl hexanediol does not require scheduling control when in human use preparations as the only health concern is eye irritancy (developmental toxicity has been shown to no longer be an issue); and
- Salts and derivatives should be specifically excluded due to difficulty in interpreting which substances are meant to be captured by the Poisons Standard entry (no examples of inappropriately captured substances were given).

#### ***Delegate's final decision***

The delegate notes the submission, however as ethyl hexanediol is to be down-scheduled from Schedule 10, it is inappropriate that all uses except for cosmetic use are exempt from scheduling. This may be reconsidered if new data is provided to the delegate and committee. Furthermore, due to the chemical structure of ethyl hexanediol, and the presence of hydroxy groups within the structure, salts and derivatives should be captured by this entry.

The delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is that the current Schedule 10 and 4 entries for ethyl hexanediol be deleted and that a new Schedule 6 entry be created. The implementation date is **1 October 2017**.

## **3.2 Climbazole**

#### ***Referred scheduling proposal***

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to amend the current entries for climbazole in Schedules 5 and 6, to restrict its use in cosmetic products except at concentrations below 0.5% in leave-on hair and face cosmetics, and up to 2% for rinse-off hair cosmetics.

### ***Current scheduling status***

Climbazole is in Schedule 5 and Schedule 6 of the Poisons Standard as follows:

#### **Schedule 6**

CLIMBAZOLE **except:**

- a) when included in Schedule 5; or
- b) in preparations containing 2 per cent or less of climbazole.

#### **Schedule 5**

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except** in preparations containing 2 per cent or less of climbazole.

Climbazole is also listed in Appendix E as follows:

#### **Appendix E, Part 2**

CLIMBAZOLE

Standard statement: 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)).

### ***Scheduling history***

Climbazole was first considered for scheduling by the Poisons Schedule Committee (PSC) in November 1980. Although the original application specified use as a household and industrial fungicide, at that time the committee decided that the absence of chronic toxicological data warranted restrictions for human use, and that Schedule 4 was appropriate.

In November 1985 the Poisons Schedule Committee (PSC) considered rescheduling climbazole from Schedule 4 to Schedule 5 (for human use), to permit its use in an antidandruff shampoo. However, the committee did not accept this rescheduling application given the lack of chronic toxicological data.

In November 1986 the Drugs and Poisons Scheduling Committee (DPSC) considered an amended application to the one received in November 1985 to reschedule climbazole from Schedule 4 to Schedule 5 (for human use) in order to permit its use in an antidandruff shampoo. In its deliberations, the committee noted that climbazole would be incorporated into the proposed Australian Cosmetic Standard at 0.5% or less. The committee agreed to delete the Schedule 4 entry for climbazole and create: a new Schedule 5 entry for preparations containing 40% or less except in preparations containing 2% or less (as in the current Schedule 5 entry); and a new Schedule 6 entry with an exemption for preparations containing 2% or less of climbazole (as in the current Schedule 6 entry).

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

#### **Schedule 6 – Amend Entry**

CLIMBAZOLE **except:**

- a) when included in Schedule 5; or
- b) **in leave-on hair and face cosmetic preparations containing 0.5 per cent or less of climbazole; or in preparations containing 2 per cent or less of climbazole.**
- c) **in rinse-off hair and face cosmetic preparations containing 2 per cent or less of climbazole.**

## Schedule 5 – Amend Entry

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole ~~except in preparations containing 2 per cent or less of climbazole:~~

- a) in leave-on hair and face cosmetic preparations containing 0.5 per cent or less of climbazole; or
- b) in rinse-off hair and face cosmetic preparations containing 2 per cent or less of climbazole.

The applicant's reasons for the request are:

- Climbazole is readily bioavailable following oral exposure and has moderate acute oral toxicity;
- Climbazole is not an eye irritant at 0.5% and not a skin irritant at 2%;
- Climbazole has been selected as a candidate for the European Union (EU) Community Action Rolling Plan (CoRAP) initiative for further evaluation of reproductive and developmental toxicity;
- Climbazole is reported to be used in cosmetic products overseas (as a preservative or antimicrobial agent); in the absence of Australian specific data, this is assumed to be representative of its use in Australia; and
- According to the SCCP Opinion (2009), climbazole is 'regulated in the Cosmetics Directive as a preservative in Annex [V], with a maximum authorized concentration of 0.5%' and 'is used as an anti-dandruff active agent in hair cosmetic preparations up to a maximum concentration of 2.0% in rinse-off products or up to a maximum concentration of 0.5% in leave-on products. In addition, it is used in leave-on face creams up to a maximum concentration of 0.5%'.

### ***Australian regulatory information***

Climbazole is permitted to be used as both an excipient and active ingredient in biological and prescription medicines; however a search of the Australian Register of Therapeutic Goods (ARTG) found it is not currently used in any listed products.

Climbazole is not listed on the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#).

The use of climbazole was approved by the Medicines Evaluation Committee (MEC) in 2004 for dermal use only. Climbazole can be used in hair care products at concentration of up to 0.5% for leave-on products and up to 2% for rinse-off products.

### ***International regulations***

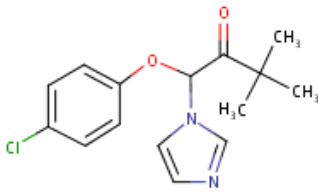
Climbazole is listed on the EU Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products. The maximum concentration allowed is 0.5% in ready for use preparations.

The SCCS has concluded (SCCS 2013) that climbazole 'may be used as a preservative (or non-preservative) ingredient up to a maximum concentration of 0.5% in leave-on hair and face cosmetics. Its non-preservative use in rinse-off hair cosmetics up to a maximum concentration of 2% was also considered to be safe. Its use in leave-on products other than those mentioned above was, however, not considered safe'. Furthermore, 'the non-preservative use of Climbazole either in foot care cosmetics alone at a concentration of up to 0.5% or in combination with either shampoo (at a maximum concentration of 2%) or face cream (at a maximum concentration of up to 0.5%) or with hair lotion (at a maximum concentration of up to 0.5%), does not pose a risk to the health of the consumer. In the case, however, that 3 products, although each safe when used separately, are combined, the combinations of either shampoo, hair lotion and a foot care product or face cream, hair lotion and a foot care product (all containing Climbazole at the maximum requested concentration) cannot be considered safe for the consumer'.

### Substance summary

Climbazole is an imidazole topical antifungal agent commonly used in the treatment of human fungal skin infections such as dandruff, eczema and Seborrheic dermatitis.<sup>43, 44</sup>

**Table 3.2A: Chemical information for climbazole**

Property	Climbazole
CAS name	2-butanone, 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethyl-
CAS number	38083-17-9
Chemical structure	
IUPAC and/or common and/or other names	climbazole (INCI and AAN); Crinipan AD; Baypival; (RS)-1-(4-Chlorophenoxy)-1-imidazol-1-yl-3,3-dimethylbutan-2-one (IUPAC); 1-[(4-chlorophenoxy)(tert-butylcarbonyl)methyl; 1-(4-chlorophenoxy)-1-(1H-imidazolyl)-3,3-dimethyl-2-butanone
Molecular formula	C <sub>15</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>
Molecular weight	292.76 g/mol

The following data was extracted from the [NICNAS IMAP Human Health Tier II report for climbazole](#).

**Table 3.2B: Acute toxicity end-points for climbazole**

Toxicity	Species	Climbazole	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Mouse (male CF1/W68)	664	Schedule 6
	Rat (Wistar)	400	
	Rabbit (female Chinchilla)	250	
	Dog (Beagle)	250–500	
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>5000	Schedule 5

<sup>43</sup> Pérez-Rivera, Alex A., et al. "Evaluation of the genotoxicity of the imidazole antifungal climbazole: comparison to published results for other azole compounds." *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* 672.1 (2009): 27-39.

<sup>44</sup> Youn H, Kim S, Ahn K, et al. Efficacy and Safety of Cream Containing Climbazole/Piroctone Olamine for Facial Seborrheic Dermatitis: A Single-Center, Open-Label Split-Face Clinical Study. *Annals Of Dermatology* [serial online]. December 2016;28(6):733-739



Toxicity	Species	Climbazole	SPF (2015) Classification
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	N/A	No data	N/A
Skin irritation	Rabbit	Slightly irritating at 0.5% concentration	Limited data
	Guinea pig	Irritating at 10% concentration	
	Human volunteers	Not a skin irritant at 2% concentration	
Eye irritation	Rabbit	Not irritating at 0.5% concentration	Limited data
	Chicken Enucleated Eye Test	Negative results up to 2% concentration	
	Hen's Egg Test-Chorioallantoic Membrane (HET-CAM) assay	Negative results for the neat chemical	
Skin sensitisation	Mouse (LLNA)	Not sensitising	N/A
	Guinea pig (GPMT)		
	Guinea pig (Buehler)		

#### *Acute toxicity*

Based on the available data, climbazole has moderate acute oral toxicity and low acute dermal toxicity. No data is available for acute inhalation toxicity.

#### *Skin irritation*

No skin irritation data are available using neat climbazole however, climbazole at 0.5% concentration was slightly irritating to the skin of New Zealand White rabbits, and an irritant in female Bor:DHPW guinea pigs at 10% concentration. In patch tests, climbazole was not a skin irritant at 2% concentration in human volunteers (SCCP 2009).

#### *Eye irritation*

No *in vivo* eye irritation studies are available using neat climbazole, however climbazole was not irritating to rabbit eyes at 0.5% concentration. A Chicken Enucleated Eye Test (screening assay) gave negative results for climbazole up to 2% concentration. A Hen's Egg Test-Chorioallantoic Membrane (HET-CAM) assay showed negative results for neat climbazole; however, this assay detects only strong eye irritants (SCCP 2009).

Climbazole is not expected to be an eye irritant in humans at 2% concentration (SCCP 2009).

#### *Skin sensitisation*

Based on the results of a local lymph node assay (LLNA) in CBA/J mice (OECD TG 429), climbazole up to 20% concentration does not have potential to induce skin sensitisation (SCCP 2009).

Climbazole gave negative results for skin sensitisation in two non-guideline studies (Magnusson Kligman Guinea Pig Maximisation test and Buehler test) in female guinea pigs (Bor:DHPW and

Hartley). [However, it should be noted that the SCCP report stated that these studies were either not valid or impossible to assess.]

#### *Repeat-dose toxicity*

Based on the available data in rats and dogs, climbazole is not considered to cause severe effects following repeated oral or inhalation exposure. However, repeated dose oral toxicity studies in rats showed increased liver enzyme activity from doses at or above 15 mg/kg bw/day. No data are available on repeated dose dermal toxicity.

The SCCP report stated that the available studies were conducted between 1975 and 1983, before GLP-regulations were in place. The descriptions were brief and the raw data incomplete. For ethical reasons and after a thorough re-examination of the available information, the SCCP proposed to accept the use of a cautious NOEL-value of 5 mg/kg bw/day, deduced from the 90 day oral study with the rat. This No observed effect level (NOEL) was used in the margin of safety (MoS) calculations for the specific use scenarios of climbazole.

The SCCP report calculated the MoS to be 701 for a 60 kg person using an anti-dandruff shampoo containing 2% climbazole, using an *in vitro* dermal penetration rate of 0.297 µg/cm<sup>2</sup> (0.15%) through human skin. This indicates that climbazole at 2% is safe for use in anti-dandruff shampoo (rinse-off products). The MoS for a 60 kg person using hair lotions, face cream and leave-on body lotion (all containing 0.5% climbazole) were calculated to be 189, 425 and 13, respectively, using *in vitro* dermal penetration rates of 1.10 µg/cm<sup>2</sup> (2.23%) or 1.25 µg/cm<sup>2</sup> (3.46%) through pig skin. Considering these MoS values, using a leave-on body lotion containing 0.5% climbazole for whole body (area of 18,000 cm<sup>2</sup>) was not considered safe as the MoS was calculated to be <100. The SCCP concluded that, 'To generate an acceptable MoS (≥ 100), the treated surface area for leave-on products containing 0.5% Climbazole should not exceed 2400 cm<sup>2</sup>.'

#### *Genotoxicity*

Based on the results from the available *in vitro* and *in vivo* genotoxicity studies, climbazole is not considered to be genotoxic. Some *in vitro* genotoxicity tests indicated positive results, but all *in vivo* tests were negative.

#### *Reproduction and developmental toxicity*

Based on the available data, climbazole is not considered to cause specific reproductive or developmental toxicity, as effects were only observed secondary to maternal toxicity. However, climbazole is a candidate for the EU CoRAP initiative for further evaluation of reproductive and developmental toxicity.

#### *Public exposure*

Climbazole is reported to be used in cosmetic products overseas as a preservative or antimicrobial agent. In the absence of Australian specific data, this is assumed to be representative of its use in Australia.

#### ***Pre-meeting public submissions***

Two (2) public submissions were received. Both submissions did not support the proposal. The submissions noted that there should be alignment with EU regulations for use in cosmetics but special consideration should then be made for domestic preparations. Currently EU regulations permits up to 0.5% in cosmetics; however there is ongoing assessment by the SCCS in Europe and therefore the rescheduling should be deferred until a decision is made by the SCCS in Europe. A delayed Poisons Standard entry of 12 months to allow implementation was requested.

The [public submissions](#) will be made available on the TGA website.

### ***Summary of ACCS advice to the delegate***

The committee recommends that the current Schedule 6 and 5 entries for climbazole be amended as follows:

#### **Schedule 6 – Amend Entry**

CLIMBAZOLE **except:**

- a) when included in Schedule 5; or
- b) ~~in preparations containing 2 per cent or less of climbazole~~ **in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or**
- c) **in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.**

#### **Schedule 5 – Amend Entry**

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except** ~~in preparations containing 2 per cent or less of climbazole:~~

- a) **in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or**
- b) **in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.**

The committee also recommended an implementation date of **1 June 2018** to allow adequate time for industry to make the necessary labelling changes.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- Climbazole is an effective fungicidal preservative.
- Moderate acute oral and low acute dermal toxicity, but high dermal absorption.
- There is a risk of toxicity if climbazole is used at concentrations up to the maximum unscheduled cut-off and/or simultaneous use of multiple preparations for different purposes; especially if preparations are intended to be left on the skin/hair. However this risk can be mitigated by the reduced exposure dermally for exempted products.

#### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to amend the current Schedule 6 and 5 entries for climbazole. The proposed Schedule entry is as follows:

#### **Schedule 6 – Amend Entry**

CLIMBAZOLE **except:**

- a) when included in Schedule 5; or
- b) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or
- c) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.

#### **Schedule 5 – Amend Entry**

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except:**

- a) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or
- b) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.

The proposed implementation date is **1 June 2018**.

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 a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Climbazole is an effective fungicidal preservative.
- Moderate acute oral and low acute dermal toxicity, but high dermal absorption.
- There is a risk of toxicity if climbazole is used at concentrations up to the maximum unscheduled cut-off and/or simultaneous use of multiple preparations for different purposes; especially if preparations are intended to be left on the skin/hair. However this risk can be mitigated by the reduced exposure dermally for exempted products.
- A long implementation date is proposed in order to allow adequate time for industry to make the necessary labelling changes.

### ***Public submissions on the interim decision***

One (1) submission was received that had no objections to the decision but suggested the decision be deferred until the the 2013 EU SCCS opinion is translated into EU regulation, due to the potential for reconsideration of the SCCS opinion. A safety assessment of the unsafe exposure scenarios highlighted in the 2013 SCCS opinion is currently being undertaken in the EU.

### ***Delegate's Final decision***

The delegate notes the submission; however, as no new evidence has been received to alter the interim decision, the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate notes that if the SCCS opinion is updated with the outcomes of the safety assessment review of the currently unsafe exposure scenarios, then climbazole could be reconsidered by the delegate and committee.

The delegate's final decision is to amend the current Schedule 6 and 5 entries for climbazole. The implementation date is **1 June 2018**.

### 3.3 *m*-Aminophenol

#### *Referred scheduling proposal*

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for *m*-aminophenol with an appropriate exemption cut-off for hair dye use.

#### *Current scheduling status and relevant scheduling history*

*m*-Aminophenol is not currently scheduled.

In August 2016, NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) Scheme submitted a proposal to create a new entry for *m*-aminophenol in Schedule 6 for restriction in cosmetic and domestic products. Prior to this date, *m*-aminophenol was unscheduled and had not previously been considered for scheduling.

In January 2017, the delegate made a [delegate-only final decision](#) to enter *m*-aminophenol in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

#### **Schedule 6**

*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 implementation date of this decision was 1 February 2017.

Following the release of the final decision on 16 January 2017, feedback from industry indicated that the wording of the Schedule 6 entry may require further amendment.

On 31 January 2017, the Schedule 6 entry for *m*-aminophenol was removed by amendment from the 1 February 2017 Poisons Standard. This [final decision](#) was implemented as [Amendment No. 1 of SUSMP 16](#). *m*-Aminophenol was subsequently [referred to the March 2017 ACCS meeting](#) to enable a consultation process on the proposed scheduling.

An isomer of *m*-aminophenol, *p*-aminophenol is in Schedule 6 and Appendices E and F of the Poisons Standard 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 (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

### Appendix F, Part 3

#### *p*-AMINOPHENOL

Warning Statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

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

*Current schedule of related substance 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 (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**

### **4-AMINO-*m*-CRESOL**

Warning statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

*Current schedule of related substance 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 (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**

### **4-AMINO-2-HYDROXYTOLUENE**

Warning statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

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### 4-AMINO-2-HYDROXYTOLUENE

Schedule 6

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### 5-AMINO-*o*-CRESOL

cross reference: 4-AMINO-2-HYDROXYTOLUENE

## *Scheduling application*

This was a general application. The applicant'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 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 – New Entry**

*m*-AMINOPHENOL

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

### **Appendix F, Part 3– New Entry**

*m*-AMINOPHENOL

Warning statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- Currently, there are no restrictions on introducing or using *m*-aminophenol 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 *m*-aminophenol 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 sensitizer 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 *m*-aminophenol 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.

### ***Australian regulatory information***

*m*-Aminophenol is listed on the [Australian Inventory of Chemical Substances \(AICS\)](#). Currently there are no restrictions on the use of *m*-aminophenol in cosmetics or domestic products in Australia. *m*-Aminophenol is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#) and a search of the Australian Register of Therapeutic Goods (ARTG) found it is not an ingredient in any listed products.

### ***International regulations***

Use of *m*-aminophenol 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 *m*-aminophenol 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 *m*-aminophenol is present at lower concentrations, sensitisation labelling is required.

Use of *m*-aminophenol 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 *m*-aminophenol in hair dyes is restricted to a maximum concentration of 1.2% applied to hair after mixing under oxidative conditions.

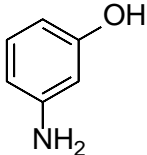
### ***Substance summary***

*m*-Aminophenol is used in hair colourants and is an important starting material for dyes, including a variety of latent dyes used in imaging technology, optical bleaches and fluorescent agents, drugs, agricultural chemicals and high performance polymers.<sup>45</sup>

**Table 3.3A: Chemical information**

Property	<i>m</i> -aminophenol
CAS names	Phenol, 3-amino
CAS numbers	591-27-5

<sup>45</sup> Dressler, H. (1994) 'm-Aminophenol', *Resorcinol: Its Uses and Derivatives*, Springer US, p 125-134.

Property	<i>m</i> -aminophenol
Chemical structure	
IUPAC and/or common and/or other names	3-hydroxyaniline <i>m</i> -aminophenol (INCI)
Molecular formula	C <sub>6</sub> H <sub>7</sub> NO
Molecular weight	109.13 g/mol

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](#).

**Table 3.3B: Acute toxicity end-points for *m*-aminophenol**

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bodyweight (bw))	Rat	812-1000	Schedule 6
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	1162	Schedule 6
Skin irritation	Rabbit	No irritation (2% <i>m</i> -aminophenol in a suspension of 0.5% methylcellulose in purified water)	N/A
Eye irritation	Rabbit	Mild irritation (2% <i>m</i> -aminophenol in a suspension of 0.5% methylcellulose in purified water)	N/A
Skin sensitisation	Mouse (LLNA) Guinea pig (GPMT)	Moderate to strong skin sensitiser (EC3 0.24-3.2%) Sensitiser. Positive reactions in 100% of animals tested at 5%, following 1% intradermal induction and 10% topical induction.	Schedule 6

### *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 *m*-aminophenol is not irritating to the skin or eyes.

### *Sensitisation*

Based on the available animal and human data, *m*-aminophenol 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 *m*-aminophenol 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 *m*-aminophenol 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 *m*-aminophenol.
- In another mouse LLNA study, CBA/Ca mice were administered *m*-aminophenol 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 *m*-aminophenol 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 *m*-aminophenol 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 *m*-aminophenol 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 *m*-aminophenol.

### ***Pre-meeting public submissions***

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for *m*-aminophenol. The main points were:

- The scheduling of *m*-Aminophenol should align with regulations in other international jurisdictions, such as the EU.
- *m*-Aminophenol is used in approximately 85-95% of hair dye products in Australia.

An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

The [public submissions](#) will be made available on the TGA website.

### ***Summary of ACCS advice to the delegate***

The committee advised that a new Schedule 6 entry for *m*-aminophenol be created as follows:

#### **Schedule 6 – New Entry**

*m*-AMINOPHENOL except when used in hair dye and eyebrow/eyelash preparations 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.

The committee recommends Appendix E/F entries be created as follows:

#### **Appendix E, Part 2 – New Entry**

##### *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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

#### **Appendix F, Part 3 – New Entry**

##### *m*-AMINOPHENOL

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

Safety directions: 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist).

The committee also recommended an implementation date of **1 June 2018** to allow for the necessary labelling changes to be implemented by industry.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- *m*-Aminophenol is a strong to moderate skin sensitiser.
- The primary consumer use of *m*-aminophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However, risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of *m*-aminophenol are consistent with the factors for Schedule 6.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to create a new Schedule 6 entry for *m*-aminophenol. The proposed Schedule entry is as follows:

#### **Schedule 6 – New Entry**

*m*-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash preparations 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 – New Entry**

*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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

## **Appendix F, Part 3 – New Entry**

### *m*-AMINOPHENOL

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

Safety directions: 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist).

The proposed implementation date is **1 June 2018**.

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

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- *m*-Aminophenol is a strong to moderate skin sensitiser.
- The primary consumer use of *m*-aminophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However, risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of *m*-aminophenol are consistent with the factors for Schedule 6.
- A long implementation date is proposed in order to allow for the necessary labelling changes to be implemented by industry.

### ***Public submissions on the interim decision***

One (1) submission was received that supported the delegate's interim decision as it is in line with the EU regulations EC No. 1223/2009. The submitter however, requests that salts and derivatives are exempt from the schedule entry due to difficulty in interpreting which substances are meant to be captured by the Poisons Standard entry (no examples of inappropriately captured substances were given).

### ***Delegate's final decision***

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

The delegate's final decision is to create a new Schedule 6 entry for *m*-aminophenol. The implementation date is **1 June 2018**.

## **3.4 2-Chloro-6-(ethylamino)-4-nitrophenol**

### ***Referred scheduling proposal***

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for 2-chloro-6-(ethylamino)-4-nitrophenol to restrict its use in hair dyes and to determine an appropriate exemption concentration cut-off.

### ***Current scheduling status and relevant scheduling history***

2-Chloro-6-(ethylamino)-4-nitrophenol is not currently scheduled.

On 16 January 2017, the delegate made a [delegate-only final decision](#) to enter 2-chloro-6-(ethylamino)-4-nitrophenol in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

#### **Schedule 6**

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 implementation date of this decision was 1 February 2017.

Following the release of the final decision on 16 January 2017, industry feedback indicated that the wording of the Schedule 6 entry may require further amendment. On 31 January 2017, the Schedule 6 entry for 2-chloro-6-(ethylamino)-4-nitrophenol was removed (by amendment) from the 1 February 2017 Poisons Standard. This [final decision](#) was implemented as [Amendment No. 1 of SUSMP 16](#). 2-Chloro-6-(ethylamino)-4-nitrophenol was subsequently [referred to the March 2017 ACCS meeting](#) to enable a consultation process on the proposed scheduling.

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard 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 3 per cent for ready-for-use preparations and 1.5 % 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 – New Entry**

##### **2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL**

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

#### **Appendix F – New Entry**

##### **2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL**

Warning statement: 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.

#### ***Australian regulatory information***

2-Chloro-6-(ethylamino)-4-nitrophenol is present on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

2-Chloro-6-(ethylamino)-4-nitrophenol is not listed on the [Therapeutic Goods \(Permissible Ingredients, 26BB\) Determination No. 1 of 2017](#) and a search of the [Australian Register of Therapeutic Goods \(ARTG\)](#) found it not listed in any products.

#### ***International regulations***

Use of 2-chloro-6-(ethylamino)-4-nitrophenol 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). 2-Chloro-6-(ethylamino)-4-nitrophenol 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 2-chloro-6-(ethylamino)-4-nitrophenol.

Use of 2-chloro-6-(ethylamino)-4-nitrophenol 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-

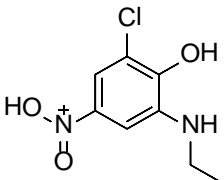


oxidising (semi-permanent) colouring agents for hair dyeing, the maximum concentration applied to hair must not exceed 1.5% for both permanent and semi-permanent application types.

### Substance summary

2-Chloro-6-(ethylamino)-4-nitrophenol has reported cosmetic use as an ingredient in both permanent and semi-permanent hair dyes in Australia and internationally.

**Table 3.4A: Chemical information**

Property	2-chloro-6-(ethylamino)-4-nitrophenol
CAS names	Phenol, 2-chloro-6-(ethylamino)-4-nitro-
CAS numbers	131657-78-8
Chemical structure	
IUPAC and/or common and/or other names	2-Chloro-6-(ethylamino)-4-nitrophenol (INCI and IUPAC)
Molecular formula	C <sub>8</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>3</sub>
Molecular weight	216.62 g/mol

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

**Table 3.4B: Acute toxicity end-points for 2-chloro-6-(ethylamino)-4-nitrophenol**

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	1728	Schedule 6
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	-	No data	N/A
Skin irritation	Rabbit	Not irritating to the skin	N/A
Eye irritation	Rabbit	Insufficient data.	N/A
Skin sensitisation (Local lymph node assay, 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, 2-chloro-6-(ethylamino)-4-nitrophenol 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, 2-chloro-6-(ethylamino)-4-nitrophenol is not considered to be genotoxic.

### *Carcinogenicity*

No animal toxicity data are available on the carcinogenicity of 2-chloro-6-(ethylamino)-4-nitrophenol. Based on the available genotoxicity data and mechanistic information, 2-chloro-6-(ethylamino)-4-nitrophenol is not considered to be carcinogenic.

### *Reproduction and developmental toxicity*

Based on the available information, 2-chloro-6-(ethylamino)-4-nitrophenol is not expected to be a developmental toxin. No reliable data examining the effect of 2-chloro-6-(ethylamino)-4-nitrophenol on fertility are available.

### *Observation in humans*

No information was available.

### *Public exposure*

Considering that 2-chloro-6-(ethylamino)-4-nitrophenol is reported to be used in hair dye products in Australia, the main route of public exposure is expected to be dermal.

### ***Pre-meeting public submissions***

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for 2-chloro-6-(ethylamino)-4-nitrophenol. The main points were:

- Scheduling of 2-chloro-6-(ethylamino)-4-nitrophenol should align with regulations in other international jurisdictions, such as the EU.
- 2-chloro-6-(ethylamino)-4-nitrophenol substance is used in the approximately 24% of hair dye products in Australia.
- An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.

The [public submission](#) is available on the TGA website.

### ***Summary of ACCS advice to the delegate***

The committee advised that a new Schedule 6 entry for 2-chloro-6-(ethylamino)-4-nitrophenol be created as follows:

#### **Schedule 6 – New Entry**

##### **2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL *except:***

- a) in non-oxidative hair dye preparations containing 3 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol 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, and

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

- b) in oxidative hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol 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, and

written in letters not less than 1.5 mm in height.

The committee recommends Appendix E/F entries be created as follows:

#### **Appendix E, Part 2 – New Entry**

##### **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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

#### **Appendix F, Part 3 – New Entry**

## 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

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

Safety directions: 4 (Avoid contact with skin).

The committee also recommended an implementation date of **1 June 2018** to allow for the necessary labelling changes to be implemented by industry.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- 2-Chloro-6-(ethylamino)-4-nitrophenol is a strong to moderate skin sensitiser.
- Primary consumer use of 2-chloro-6-(ethylamino)-4-nitrophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2-chloro-6-(ethylamino)-4-nitrophenol are consistent with the factors for Schedule 6.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to create new Schedule 6 and Appendix E/F entries for 2-chloro-6-(ethylamino)-4-nitrophenol. The proposed Schedule entry is as follows:

#### **Schedule 6 – New Entry**

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except:**

- a) in non-oxidative hair dye preparations containing 3 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol 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, and

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

- b) in oxidative hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol 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, and

written in letters not less than 1.5 mm in height.

### **Appendix E, Part 2 – New Entry**

#### **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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

### **Appendix F, Part 3 – New Entry**

#### **2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL**

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

Safety directions: 4 (Avoid contact with skin).

The proposed implementation date is **1 June 2018**. This implementation date is proposed in order to allow for the necessary labelling changes to be implemented by industry.

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

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- 2-Chloro-6-(ethylamino)-4-nitrophenol is a strong to moderate skin sensitiser.
- Primary consumer use of 2-chloro-6-(ethylamino)-4-nitrophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2-chloro-6-(ethylamino)-4-nitrophenol are consistent with the factors for Schedule 6.

### ***Public submissions on the interim decision***

One (1) submission was received that supported the delegate's interim decision, as it is in line with the EU regulations EC No. 1223/2009. The submitter however, requests that salts and derivatives are exempt from the schedule entry due to difficulty in interpreting which substances are meant to be captured by the Poisons Standard entry (no examples of inappropriately captured substances were given).

### ***Delegate's final decision***

The delegate notes the submission; however, as no new evidence has been received to alter the interim decision, the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to create new Schedule 6 and Appendix E/F entries for 2-chloro-6-(ethylamino)-4-nitrophenol. The implementation date is **1 June 2018**.

### 3.5 2,4-Diaminophenoxyethanol

#### *Referred scheduling proposal*

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a Schedule 6 entry for 2,4-diaminophenoxyethanol with appropriate concentration cut-off for use in hair dyes.

#### *Current scheduling status*

2,4-Diaminophenoxyethanol is currently in Schedule 6 and Appendices E and F 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 dyeing 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).

#### *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.

In August 2016, NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) Scheme submitted a proposal to create a new Schedule 6 entry [*Secretariat note: an entry already exists*] for 2,4-diaminophenoxyethanol except when used in hair dye and eyebrow/eyelash colouring

products at a concentration of 2 per cent or less after mixing for use when the immediate container and primary pack are labelled appropriately.

On 16 January 2017, the delegate made a [delegate-only final decision](#) to amend the Schedule 6 entry for 2,4-diaminophenoxyethanol as follows:

### **Schedule 6**

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.

The delegate also amended the Appendix F, Part 3 warning statement from 21<sup>46</sup> to 28.<sup>47</sup>

### ***Scheduling application***

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

### **Schedule 6**

ETHANOL, 2-(2,4-DIAMINOPHENOXY)-, DIHYDROCHLORIDE **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 2 per cent or less of Ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride 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.

### **Appendix E, Part 2**

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<sup>46</sup> (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).

<sup>47</sup> ((Over) (repeated) exposure may cause sensitisation).

## ETHANOL, 2-(2,4-DIAMINOPHENOXY)-, DIHYDROCHLORIDE

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

## ETHANOL, 2-(2,4-DIAMINOPHENOXY)-, DIHYDROCHLORIDE

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

The applicant's reasons for the request are:

- 2,4-Diaminophenoxyethanol dihydrochloride 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 dihydrochloride has reported cosmetic use in permanent hair dye preparations in Australia;
- 2,4-diaminophenoxyethanol dihydrochloride 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 dihydrochloride at any concentration; and
- When 2,4-diaminophenoxyethanol dihydrochloride 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.

### *Australian regulatory information*

2,4-Diaminophenoxyethanol dihydrochloride 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).

2,4-Diaminophenoxyethanol dihydrochloride is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017.

A search of the Australian Register of Therapeutic Goods (ARTG) found 2,4-diaminophenoxyethanol dihydrochloride not in any listed products.

### *International regulations*

The Association of South East Asian Nations (ASEAN), Canada, New Zealand and the European Union (EU) have restricted the use of 2,4-diaminophenoxyethanol in cosmetics. Following a safety evaluation, the Scientific Committee on Consumer Products (SCCP) concluded that the use of 2,4-diaminophenoxyethanol '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).

2,4-Diaminophenoxyethanol 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



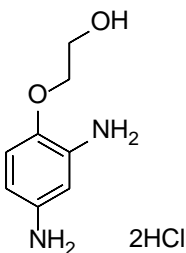
contain except subject to the restrictions laid down: 'After mixing under oxidative conditions the maximum concentration applied to hair or eyelashes must not exceed 2.0% (as hydrochloride) and for professional use only'. The Cosmetic Regulation also mandates label warning statements relating to the sensitisation potential of 2,4-diaminophenoxyethanol;

- 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').

### Substance summary

2,4-Diaminophenoxyethanol is a light grey to light pink (dihydrochloride) or white powder (sulfate) used primarily in hair dye formulations.

**Table 3.5A: Chemical information**

Property	2,4-diaminophenoxyethanol dihydrochloride
CAS names	ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride
CAS numbers	66422-95-5
Chemical structure	
IUPAC and/or common and/or other names	2,4-diaminophenoxyethanol HCL (INCI); 2-(2,4-diaminophenoxy)ethanol dihydrochloride (IUPAC).
Molecular formula	C <sub>8</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>
Molecular weight	241.1 g/mol

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

**Table 3.5B: Acute toxicity end-points for 2-(2,4-diaminophenoxy)ethanol dihydrochloride**

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	1000	Schedule 6
	Mouse	1160	

Toxicity	Species	Result	SPF (2015) Classification
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /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*

2,4-Diaminophenoxyethanol is considered to have moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD<sub>50</sub>) 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, 2,4-diaminophenoxyethanol is not considered to be a skin irritant.

#### *Eye Irritation*

Based on the available data, 2,4-diaminophenoxyethanol 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 dihydrochloride was instilled into the conjunctival sac of the left eye of each animal. The eyes were not rinsed following instillation of 2,4-diaminophenoxyethanol. 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 2,4-diaminophenoxyethanol did not produce any irritation.

#### *Sensitisation*

Based on the available data, 2,4-diaminophenoxyethanol 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). 2,4-Diaminophenoxyethanol 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 dihydrochloride 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, 2,4-diaminophenoxyethanol are not expected to be genotoxic.

### *Carcinogenicity*

Based on the available data, 2,4-diaminophenoxyethanol is not considered to be carcinogenic.

### *Reproduction and developmental toxicity*

Based on the available data, 2,4-diaminophenoxyethanol is not expected to have reproductive and developmental toxicity.

### ***Pre-meeting submissions***

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for 2,4-diaminophenoxyethanol. The main points were:

- Scheduling of 2,4-diaminophenoxy-ethanol should align with regulations in other international jurisdictions, such as the EU.
- 2,4-Diaminophenoxy-ethanol is used in approximately 70-95% of hair dye products in Australia.
- An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.

The [public submission](#) is available on the TGA website.

### ***Summary of ACCS advice to the delegate***

The committee advised that the Schedule 6 and Appendix E/F entries for 2,4-diaminophenoxyethanol be amended as follows:

#### **Schedule 6 – Amend Entry**

2,4-DIAMINOPHENOXYETHANOL in hair dye preparations ~~except in preparations containing 4~~  
**except when used in hair dye and eyebrow/eyelash preparations at a concentration of 2** per cent  
or less of 2,4-diaminophenoxyethanol 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 – Amend Entry**

##### **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.);~~ E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.); S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

## Appendix F, Part 3 – Amend Entry

### 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);~~ 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).

The committee also advised an implementation date of **1 June 2018** to allow industry to make the necessary changes to labelling.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- 2,4-Diaminophenoxyethanol is a strong to moderate skin sensitiser.
- Primary consumer use of 2,4-diaminophenoxyethanol is in hair dye and eyelash dye products. Although dermal contact of 2,4-diaminophenoxyethanol is unavoidable when used in hair dye preparations, risk can be appropriately managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2,4-diaminophenoxyethanol is consistent with the factors for Schedule 6.
- 2,4-Diaminophenoxyethanol is an irreversible eye irritant at high concentrations.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to amend the Schedule 6 and Appendix E/F entries for 2,4-diaminophenoxyethanol. The proposed Schedule entry is as follows:

## **Schedule 6 – Amend Entry**

2,4-DIAMINOPHENOXYETHANOL **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 2 per cent or less of 2,4-diaminophenoxyethanol 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 – Amend Entry**

##### **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)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

#### **Appendix F, Part 3 – Amend Entry**

##### **2,4-DIAMINO-PHENOXYETHANOL**

Warning statement: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).

The proposed implementation date is **1 June 2018**.

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

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- 2,4-Diaminophenoxyethanol is a strong to moderate skin sensitiser.
- Primary consumer use of 2,4-diaminophenoxyethanol is in hair dye and eyelash dye products. Although dermal contact of 2,4-diaminophenoxyethanol is unavoidable when used in hair dye preparations, risk can be appropriately managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2,4-diaminophenoxyethanol is consistent with the factors for Schedule 6.
- 2,4-Diaminophenoxyethanol is an irreversible eye irritant at high concentrations.
- A long implementation date is proposed in order to allow industry to make the necessary changes to labelling.

#### **Public submissions on the interim decision**

One (1) submission was received that supported the delegate's interim decision, as it is in line with the EU regulations EC No. 1223/2009. The submitter however, requests that salts and derivatives are

exempt from the schedule entry due to difficulty in interpreting which substances are meant to be captured by the Poisons Standard entry (no examples of inappropriately captured substances were given).

### ***Delegate's final decision***

The delegate notes the submission; however, as no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to amend the Schedule 6 and Appendix E/F entries for 2,4-diaminophenoxyethanol. The implementation date is **1 June 2018**.

## **3.6 Isoeugenol**

### ***Referred scheduling proposal***

An application was initiated by the chemicals scheduling delegate to amend the Schedule 5 and Schedule 6 entries for isoeugenol to specify concentration cut-offs in products both intended and not intended for skin contact.

### ***Current scheduling status***

Isoeugenol is currently in Schedules 5 and 6 of the Poisons Standard (February 2017) as follows:

#### **Schedule 6**

ISOEUGENOL **except**:

- a) when included in Schedule 5; or
- b) in preparations containing 10 per cent or less of isoeugenol.

#### **Schedule 5**

ISOEUGENOL in preparations containing 25 per cent or less of isoeugenol **except** in preparations containing 10 per cent or less of isoeugenol.

On 1 June 2017 (foreshadowed by the delegate's final decision following the July 2016 ACCS consideration of isoeugenol), the Schedule 5 and 6 entries for isoeugenol were to be amended in the Poisons Standard; however, this implementation has not been actioned due to this current proposal to amend the scheduling entry, in consideration of the reasons for which isoeugenol is now being reconsidered.

July 2016 ACCS scheduling decision:

#### **Schedule 6**

ISOEUGENOL **except**:

- a) when included in Schedule 5; or
- b) in preparations intended for contact with skin containing 0.5 per cent or less of isoeugenol.

#### **Schedule 5**

ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol **except** in preparations intended for contact with skin containing 0.5 per cent or less of isoeugenol.

## ***Scheduling history***

Isoeugenol was first considered for scheduling in November 1996 by the NDPSC and at that time, the acute toxicity profile of isoeugenol warranted inclusion in Schedules 5 and 6 because of skin and eye irritancy, skin sensitisation potential and the oral LD<sub>50</sub>.

Isoeugenol was considered for scheduling again in July 2016 at the Advisory Committee on Chemicals Scheduling (ACCS). The committee advised that the Schedule 5 and Schedule 6 cut-off should be amended from 10% to 0.5% in preparations intended for contact with the skin due to the use pattern and skin sensitisation potential of isoeugenol. The implementation date for this decision was to be 1 June 2017.

After publication of the [July 2016 ACCS final decision](#) industry indicated that, while the exemption cut-off of 0.5% of isoeugenol in products intended for skin contact was appropriate, there should be a separate concentration cut-off for products not intended for skin contact (and that 10% was appropriate).

## ***Scheduling application***

The delegate-initiated scheduling proposal is to amend the Schedule 5 and Schedule 6 entries for isoeugenol to specify concentration cut-offs in products both intended and not intended for skin contact. Consideration has been given to the current Schedule 5 and Schedule 6 entries with a specified 10 per cent cut-off, and the previous application to amend the Schedule 5 and Schedule 6 entries for isoeugenol, with a specified 1 per cent cut-off.

The proposed changes to the Poisons Standard are:

### **Schedule 6 – Amend Entry**

ISOEUGENOL **except:**

- a) when included in Schedule 5; or
- b) in preparations **not intended for skin contact** containing 10/**1** per cent or less of isoeugenol;  
**or**
- c) **in preparations intended for skin contact containing 0.5 per cent or less of isoeugenol.**

### **Schedule 5 - Amend Entry**

ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol **except:**

- a) in preparations **not intended for skin contact** containing 10/**1** per cent or less of isoeugenol;  
**or**
- b) **in preparations intended for skin contact containing 0.5 per cent or less of isoeugenol.**

## ***Australian regulatory information***

Isoeugenol is listed on the Australian Inventory of Chemical Substances (AICS) (NICNAS, 2007). No specific Australian industrial use, import, or manufacturing information has been identified.

Isoeugenol is available for use as an Active Ingredient in: Biologicals, Prescription Medicines and is available for use as an Excipient Ingredient in: Biologicals, Devices, Listed Medicines, Prescription Medicines. Isoeugenol is permitted for use in a medicine as a flavour, at no more than 5 per cent, or a fragrance at no more 1 per cent.

Isoeugenol is not listed on the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#).

Isoeugenol is included in 171 listed products on the ARTG. The types of product vary, ranging from sunscreens and skin lotions, complementary medicines and dietary supplements, cough preparations, epilepsy drugs, anti-fungal ointments and hospital-grade disinfectants.

### ***International regulations***

Isoeugenol is listed on the following:

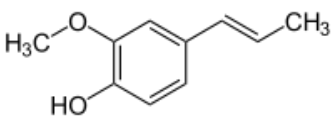
- European Union (EU) Cosmetics Regulation 76/768/EEC Annex III Part 1—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down—maximum authorised concentration in the finished cosmetic product: 0.02%; and
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.
- Based on qualitative risk assessment, the International Fragrance Association (IFRA) has indicated an acceptable concentration for isoeugenol in skin contact products should be 0.02%.

### ***Substance summary***

Isoeugenol is one of several structurally similar phenylpropenoid compounds produced by plants. It has been extracted from calamus, savoury, basil, ylang-ylang, clove, tuberose, jonquil, nutmeg, tobacco, sandalwood, dill seed, mace, gardenia, petunia, and other flowers. Isoeugenol can also be produced by isomerization of eugenol, which occurs naturally in clove, pimento, bay leaf, and cinnamon.

As a fragrance with a spicy, carnation-like odour, isoeugenol is incorporated into numerous household and personal hygiene products, including perfumes, cream lotions, soaps, and detergents. As a flavouring agent, isoeugenol is added to non-alcoholic drinks, baked foods, and chewing gums.<sup>48</sup>

**Table 3.6A: Chemical information**

Property	Isoeugenol
CAS name	phenol, 2-methoxy-4-(1-propenyl)
CAS number	97-54-1
Chemical structure	
Alternative names	2-methoxy-4-(prop-1-en-1-yl)phenol; phenol, 2-methoxy-4-(1-propenyl)
Molecular formula	C <sub>10</sub> H <sub>12</sub> O <sub>2</sub>
Molecular weight	164.2 g/mol

The following has been extracted from the [NICNAS IMAP Human Health Tier II assessment report for phenol, 2-methoxy-4-\(1-propenyl\)-](#).

<sup>48</sup> *Natl Toxicol Program Tech Rep Ser.* 2010 Sep;(551):1-178



**Table 3.6B: Acute toxicity endpoints for isoeugenol**

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	1290–1880	Schedule 6
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rabbit	1910	Schedule 6
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	N/A	N/A	N/A
Skin irritation	Rabbit	Evidence of severe irritation (non-guideline study)	Schedule 6
Eye irritation	Rabbit	Evidence of irritation	Schedule 5
Skin sensitisation (LLNA)	Various	2% (weighted mean from over 40 tests)	Schedule 6

*Acute toxicity*

Isoeugenol is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data support the existing classification for isoeugenol as ‘harmful if swallowed: (Xn; R22)’.

A review of the literature by the US National Toxicology Program (2010) found that oral LD50 values for isoeugenol ranged from 1290 to 1880 mg/kg bw for rats and 1130 to 1780 mg/kg bw for guinea pigs.

*Irritation*

The potential for isoeugenol to irritate the skin has been assessed in a number of animal studies. In a non-guideline study, undiluted isoeugenol was applied to the dorsal skin of albino Angora rabbits and guinea pigs under occlusion for 24 hours. Patches were removed and a second application was made 30 minutes later. Macro and microscopic examination of excised skin revealed evidence of severe irritation.

*Sensitisation*

Isoeugenol is considered to be a skin sensitizer based on human data, positive results seen in guinea pig maximisation tests (GPMT) and LLNAs.

The estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) was determined from over 40 separate LLNA tests conducted using isoeugenol. The weighted mean EC3 value of 2% was reported from the combined data. Lower EC3 values have been reported elsewhere in the literature, including as low as 0.54%.

In a GPMT with isoeugenol, animals were intra-dermally induced at 0.15% followed by topical induction at 25%. A challenge phase was conducted seven days later with topical application of a 5% solution. Responses were seen in 100% of animals.

Similar effects were observed when isoeugenol was tested in Freund’s complete adjuvant tests. In one test, guinea pigs (10/group) were intra-dermally induced at 1, 3 or 10% followed by a challenge using a topical application of isoeugenol at the same respective concentrations. Responses were seen in 5/10, 9/10 and 10/10 animals in the 1, 3 and 10% induction and challenge groups, respectively. In another FCA test, eight guinea pigs were intra-dermally induced at 5%, followed by a challenge by topical application at the same concentration. Responses were seen in all eight animals.

HRIPs have also indicated that isoeugenol is a skin sensitiser in humans.

#### *Repeat-dose toxicity*

The available data suggest that isoeugenol has low repeated dose toxicity, based on results from animal tests following oral exposure.

#### *Genotoxicity*

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, isoeugenol is not considered to be genotoxic. Some *in vitro* genotoxicity tests indicated weakly positive results, but all *in vivo* tests were negative.

#### *Carcinogenicity*

Isoeugenol is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40) in the HSIS (Safe Work Australia). The available data support this classification.

In a two-year carcinogenicity study, Fischer 344 (F344) rats (50/sex/group) were dosed with isoeugenol by oral gavage at 0, 75, 150, or 300 mg/kg bw, five days per week for 105 weeks. Survival rates of the exposed animals were comparable to controls. Mean body weights of males in the high dose group were increased compared with controls. Two males in the high dose group developed thymomas, while two other males in this group developed mammary gland carcinomas. Some animals in the mid and high dose groups showed olfactory epithelial metaplasia and mild atrophy of the olfactory nerves.

A similar experiment was conducted in B6C3F1 mice (50/sex/group) where animals were dosed with isoeugenol by oral gavage at 0, 75, 150 or 300 mg/kg bw, 5 days/week for 104 weeks (females) and 105 weeks (males). Survival was decreased in males in the high dose group and body weights were reduced in both males and females in this group. In all groups, males exhibited increased incidences of hepatocellular adenoma, hepatocellular carcinoma and hepatocellular carcinoma and adenoma (combined). Incidences of hepatic clear cell foci were also increased in the male mice that received 75 or 150 mg/kg bw/day. There was also a significant increase in the incidence of histiocytic sarcomas (at multiple tissue sites) in females across all groups. Olfactory epithelial metaplasia was observed in all exposed groups. Bowman's gland hyperplasia was also significantly increased in all exposed groups. Mild renal papillary necrosis and renal tubule necrosis were also significantly increased in the high dose group females. There were dose-dependent increases in the incidences of forestomach squamous hyperplasia, inflammation (statistically significant in high dose males and females) and ulceration (for high dose males only).

#### *Reproduction and developmental toxicity*

Isoeugenol does not show specific reproductive or developmental toxicity. The reproductive and developmental effects seen in studies were secondary to maternal toxicity.

#### *Public exposure*

Although the use of isoeugenol in cosmetic/domestic products in Australia is not known, it is reported to be used overseas in cosmetic products (as a perfuming agent) and domestic products (including cleaning and surface treatment products).

#### ***Pre-meeting public submissions***

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for isoeugenol. The main points were:

- Scheduling of isoeugenol should align with regulations in other international jurisdictions, such as the EU, as well as IFRA standards.

- Isoeugenol scheduling has been ambiguous and it is appreciated by industry that the wording of the Schedule 5 entry is being revisited.
- An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.

The [public submission](#) is available on the TGA website.

### **Summary of ACCS advice to the delegate**

The committee advised that the Schedule 6 and Schedule 5 entries for isoeugenol be amended as follows:

#### **Schedule 6 – Amend Entry**

ISOEUGENOL **except:**

- a) when included in Schedule 5; or
- b) in preparations **not intended for skin contact** containing 10 per cent or less of isoeugenol; **or**
- c) **in preparations intended for skin contact containing 0.02 per cent or less of isoeugenol.**

#### **Schedule 5 - Amend Entry**

ISOEUGENOL in preparations **not intended for skin contact** containing 25 per cent or less of isoeugenol **except** in preparations containing 10 per cent or less of isoeugenol.

#### **Appendix E, Part 2 – New Entry**

##### **ISOEUGENOL**

**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), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

#### **Appendix F, Part 3 – New Entry**

##### **ISOEUGENOL**

**Warning statements:** 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

**Safety directions:** 1 (Avoid contact with eyes), 4 (Avoid contact with skin).

The committee also advised an implementation date of **1 October 2017** to allow industry to make the necessary changes to product labelling.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice comprised the following:

- Isoeugenol has moderate acute toxicity consistent with Schedule 6 criteria. Isoeugenol is a skin and eye irritant at 1% and a strong sensitiser at low concentrations (EC3 0.54%). There is evidence of carcinogenicity in male mice and possible carcinogen in female mice and male rats.

- Isoeugenol is used widely internationally in a large range of products including foods, therapeutic, household and cosmetic products
- Risk can be mitigated with appropriate warning and first aid statements.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to amend Schedule 6 and Schedule 5 for isoeugenol and to create new entries for isoeugenol in Appendix E/F. The proposed Schedule entry is as follows:

#### **Schedule 6 – Amend Entry**

ISOEUGENOL **except**:

- a) when included in Schedule 5; or
- b) in preparations not intended for skin contact containing 10 per cent or less of isoeugenol; or
- c) in preparations intended for skin contact containing 0.02 per cent or less of isoeugenol.

#### **Schedule 5 – Amend Entry**

ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol **except** in preparations containing 10 per cent or less of isoeugenol.

#### **Appendix E, Part 2 – New Entry**

ISOEUGENOL

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), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

#### **Appendix F, Part 3 – New Entry**

ISOEUGENOL

Warning statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).

The proposed implementation date is **1 October 2018**.

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 a substance; (b) the purposes for which a substance is to be used 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 reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Isoeugenol has moderate acute toxicity consistent with Schedule 6 criteria. Isoeugenol is a skin and eye irritant at 1% and a strong sensitiser at low concentrations (EC3 0.54%). There is evidence of carcinogenicity in male mice and possible carcinogen in female mice and male rats.
- Isoeugenol is used widely internationally in a large range of products including foods, therapeutic, household and cosmetic products.
- Risk can be mitigated with appropriate warning and first aid statements.
- The long implementation date is proposed in order to allow industry to make the necessary changes to product labelling.

#### ***Public submissions on the interim decision***

Eight (8) public submissions were received in response to the delegate's interim decision: two (2) supported, four (4) had no objections and two (2) opposed the interim decision.

*The main points in support were:*

- The new concentration exemption cut-off of 0.02% is in alignment with the International Fragrance Association (IFRA) standard for isoeugenol;
- Isoeugenol in products on the ARTG discussed in submissions are at concentrations lower than the 0.02% exemption cut-off and are therefore unaffected.

*The main points opposed were:*

- The current IFRA Standard of use and the labelling requirements of Annex III of the EU Cosmetics Regulation should be considered as sufficient for the safe use of isoeugenol;
- Therapeutic goods should be excluded from the interim decision;
- Clarity is need for products that are not used on the skin but are used orally.

#### ***Delegate's final decision***

The delegate notes the submissions. Isoeugenol is included in 171 products on the ARTG; the TGA underwent a targeted consultation with sponsors of these products. All of the sponsors that responded indicated that the concentration of isoeugenol in their products intended for skin contact was not captured by a 0.02% or less exemption cut-off.

Skin sensitisation, dermal toxicity and skin irritation of isoeugenol are the reasons for a lower exemption cut-off for products applied to skin.

As no new evidence has been received to alter the interim decision; the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to amend Schedule 6 and Schedule 5 for isoeugenol and to create new entries for isoeugenol in Appendix E/F. the implementation date is **1 October 2018**.

### 3.7 *Aureobasidium pullulans* (strains DSM 14940 and DSM 14941)

#### *Referred scheduling proposal*

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a Schedule 5 entry for *Aureobasidium pullulans* (*A. pullulans*) (strains DSM 14940 and DSM 14941) with no exemption cut-offs.

#### *Current scheduling status and relevant scheduling history*

*A. pullulans* is not currently scheduled and has not been previously considered for scheduling; therefore a scheduling history is not available.

#### *Scheduling application*

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

##### **Schedule 5 – New Entry**

AUREOBASIDIUM PULLULANS.

The applicant's reasons for the request are:

- *A. pullulans* is a saprophytic fungus (feeding on dead and decaying organic matter) ubiquitous in the environment, readily isolated from soil, decaying vegetation, wood, air, shower curtains and other damp surfaces. Background levels of the organism on apple leaves for example are approximately 104 to 105 Colony Forming Units (CFU – i.e. viable organisms) per gram dry weight.
- The proposed fungicide consists solely of the freeze dried fermentation liquid containing the cultured strains of *A. pullulans* (DSM 14940 & 14941) and food grade constituents that act as drying and granulating aids.
- The fungicide is intended for use as a fungicide for the prevention of Botrytis cinerea infection of grapes through spray application, at a maximum rate of 1 kg/ha. XXXX contains  $5 \times 10^9$  CFU/g of *A. pullulans* mixed strains DSM14940 and DSM14941. The fungicide will be applied to vineyards as a foliar spray after dilution of the product (wetttable granule) in water by vineyard workers. The fungicide is not proposed for home garden use or for use in urban environments.
- In support of the application the applicant has submitted acute toxicity studies on a European Registered product, XXXX, which contains the same two strains at approximately  $2.5 \times 10^9$  CFU per strain making up 44%, with the balance of that product consisting of food grade non-active constituents.
- XXXX has low acute oral & dermal toxicity in rats ( $LD_{50} > 2000$  mg/kg bw and  $> 6 \times 10^9$  CFU/kg, respectively) producing no deaths or signs of toxicity or infectivity at the limit doses. A 10% suspension of XXXX in water had an  $LC_{50}$  of  $> 5170$  mg/m<sup>3</sup> with no deaths and no clinical signs of toxicity or infectivity; however the actual concentration of the product in the air was only 497 mg/m<sup>3</sup> ( $1.5 \times 10^9$  CFU /m<sup>3</sup>). XXXX was not a skin or eye irritant in rabbits but was a moderate skin sensitiser in Guinea pigs by the Buehler method. XXXX was not genotoxic in the mouse *in vivo* micronucleus assay. When XXXX was administered subcutaneously to rats at 2000 mg/kg bw ( $3 \times 10^9$  CFU/kg bw) 1/5 males had to be euthanised at day 5 due to massive inflammation at the injection site, but all other animals survived to scheduled sacrifice. In all animals, the spleen was visibly enlarged, and mature puss filled abscesses were present at the injection sites. These observations reflect both route of administration and the large quantity of foreign biological materials injected rather than infection or pathogenesis *per se*.
- *A. pullulans* strain DSM 14941 was not infectious, toxic or pathogenic when administered to rats by the oral ( $4 \times 10^8$  CFU), subcutaneous (107 CFU), or intratracheal routes ( $0.8 \times 10^8$  CFU) and viable

organisms did not persist at the site of administration or migrate to other tissues. Following intratracheal administration, viable spores were isolatable from the lungs only at 3 hours after administration but were not present at or after 3 days. Acute pulmonary inflammation was observed at 3 hrs and 3 days after application, progressing towards resolution by day 21.

- As *A. pullulans* is an ubiquitous non-pathogenic/infectious fungi that does not produce toxins or antimicrobials, studies of carcinogenicity, reproductive, developmental and neuro-toxicity are not required and have not been provided.
- When isolated from human clinical specimens *A. pullulans* is generally considered to be a laboratory contaminant, but under specific circumstances where the patient is debilitated or immune-suppressed some strains of this organism have infrequently been identified as pathogens. Pathogenic strains, where investigated, are able to grow at, or close to, body temperatures whereas strains isolated from the environment are generally unable to grow or survive at temperatures above 30 - 35°C or so, as has been shown to be the case for the two strains in the fungicide. No skin or pulmonary sensitisation or allergenic response of, or clinical findings in, any of the production or agricultural workers handling the fungus or XXXX have been observed.
- XXXX is registered in Europe and both XXXXX and XXXX have been registered in the USA. Neither jurisdiction has considered the establishment of an ADI or ARfD to be required for *Aureobasidium pullulans* DSM 14940 & 14941.

### **Australian regulatory information**

There is one product (registered medicine) on the [Australian Register of Therapeutic Goods \(ARTG\)](#) that contains *A. pullulans*. The indicated use of the product is for the diagnosis and treatment (hypo-sensitization therapy) of patients who experience allergic symptoms.

According to the TGA Ingredient database, *A. pullulans* is available for use as an Active Ingredient in Export Only, List Medicines, Over the Counter and Prescription Medicines. It is also available for use as a homeopathic ingredient in Listed Medicines and as an Excipient and Equivalent Ingredient in Prescription Medicines.<sup>49</sup>

*A. pullulans* is listed on the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 1 of 2017](#), permitted for use as an Active and Homeopathic preparation Ingredient. There are no specific requirements specified in the determination.

### **International regulations**

*A. pullulans* is registered for use as a fungicide in the USA (January 2012) and Canada (December 2012) for the control of botrytis in grapes. It is also registered in New Zealand (June 2015) for control of fire blight in pip fruit and control of *Psa* in kiwifruit.

*A. pullulans* has been registered by the European Food Safety Authority (EFSA) for control of fire blight in pome fruit with appropriate personal protective equipment (PPE) requirements.

*A. pullulans* is unclassified in New Zealand.

### **Substance summary**

The genus *Aureobasidium* includes between 14 and 26 named species depending on the consulted registry. Among these, *A. pullulans* is the only well-known species, of which two well documented varieties are associated with indoor environment and health problems: *A. pullulans* var. *pullulans* and

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<sup>49</sup> Note: Only the name and definition of a substance have been reviewed to allow it to be included in the ingredient repository. The approval for use of the ingredient in therapeutic goods is a decision made by the relevant TGA regulatory area. This approval process may require submission of further information, for example safety data for the ingredient or for the finished goods, to meet legislative and regulatory requirements.



*A. pullulans* var. *melanogenum*. On the other hand, the fungal database of the International Mycological Association lists 6 varieties of *A. pullulans*.

*Aureobasidium pullulans* is an ubiquitous saprophyte mould, which is generally considered as an environmental contaminant. It is most common in temperate zones with numerous recordings from the British Isles and the USA, but also found in Canada, Alaska, Antarctica, Europe and Russia. It is found in forest soil, freshwater, aerial portions and on leaf surfaces of plants as well as on seeds (wheat), cereals (barley, oats) and some nuts such as pecans. It is also found as spoilage agent on fruits (pears, grapes and tomatoes) or in fruit drinks. It has been associated with the deterioration of pears and oranges in storage or in transit.

*A. pullulans* is commercially used for the production of pullulan, a linear homopolysaccharide of glucose ( $\alpha$ -(1→6) maltotriose). Together with its derivatives, *Aureobasidium pullulans* has a range of uses in foods, pharmaceuticals, manufacturing, and electronics, such as un-derivatised films which readily dissolve in water and which can be used as edible food coatings.

**Table 3.7A: General information**

Property	<i>A. pullulans</i>
CAS names	N/A
CAS numbers	N/A
IUPAC and/or common and/or other names	<i>Aureobasidium pullulans</i> DSM 14940, CF10; <i>Aureobasidium pullulans</i> DSM 14941, CF40; <i>Pullularia pullulans</i> Fungus; <i>A. pullulans</i>
Approved Herbal Name (AHN)	<i>Aureobasidium pullulans</i>
Taxonomy	Kingdom: Fungi Phylum: Ascomycota Class: Dothideomycetes Order: Dothideales Family: Dothioraceae Genus: <i>Aureobasidium</i> Species: <i>Pullulans</i>

As noted previously, XXXX consists solely of the freeze dried fermentation liquid containing the cultured strains of *A. pullulans* (DSM 14940 & 14941) and food grade constituents that act as drying and granulating aids.

The strains were isolated at the University of Konstanz in 1989 from apple leaves of an untreated apple plantation (*Malus sylvestris* var. *domestica* cv. "Golden Delicious") and were designated CF10 and CF40. The manufacturing code has designated CF10 as *Aureobasidium pullulans* DSM 14940, and CF40 as *Aureobasidium pullulans* DSM 14941.



**Table 3.7B: Acute toxicity end-points for *A. pullulans* strains DSM14940 and DSM14941**

Toxicity	Species	Result <sup>50</sup>	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000 mg/kg bw	Schedule 5 / Appendix B
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000 mg/kg bw	Schedule 5 / Appendix B
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	>5170 mg/m <sup>3</sup> for a 10% suspension in water	Schedule 5 / Appendix B
Skin irritation	Rabbit	Not irritant	Nil
Eye irritation	Rabbit	Not irritant	Nil
Skin sensitisation (Buehler)	Guinea Pigs	Moderate sensitiser	Schedule 5 or Schedule 6

A technical report for the toxicology of *A. pullulans* strains DSM14940 and DSM1494 was provided to the committee and the delegate.

#### *Mutagenicity*

Not mutagenic *in vivo* (mouse micronucleus test).

#### *Public exposure*

Specific toxicity, pathogenicity and infectiveness studies were not provided.

#### ***Pre-meeting public submissions***

One (1) public submission was received, which supported the proposal due to purported low toxicological profile and that it is not an infective agent.

The [public submission](#) is available on the TGA website.

#### ***Summary of ACCS advice to the delegate***

The committee advised that a new Appendix B entry be created.

#### **Appendix B – New Entry**

#### **AUREOBASIDIUM PULLULANS (Strains DSM14940 and DSM14941)**

The committee also advised an implementation date of **1 October 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) 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 reasons for the advice comprised the following:

- There are no known cases of skin sensitisation or pulmonary hypersensitivity to the two strains of *A. pullulans* being considered.

<sup>50</sup> Based on the product, Blossom Project, containing 2 x 10<sup>9</sup> CFU/g of each of DSM14940 and 14941.

- There is a wide range of benefits from the use of pullulans manufactured using *A. pullulans*. Pullulans is used in a wide range of products including in food, cosmetics, pharmaceuticals, electronics and biomedical applications.
- The toxicity of *A. pullulans* is very low to nil with no evidence of skin or eye irritancy. *A. pullulans* is not mutagenic, pathogenic or infective and does not produce toxins or active metabolites. *A. pullulans* is a moderate skin sensitiser (Buehler method); however there are no known reports of occupational sensitisation despite industrial and farm use.
- Risk of sensitisation to *A. pullulans* can be mitigated through personal protective equipment controlled through APVMA labelling regulations.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate's interim decision is to create a new Appendix B for *Aureobasidium pullulans*. The proposed Schedule entry is as follows:

#### **Appendix B – New Entry**

AUREOBASIDIUM PULLULANS (Strains DSM14940 and DSM14941)

The proposed implementation date is **1 October 2017**.

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 a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- There are no known cases of skin sensitisation or pulmonary hypersensitivity to the two strains of *A. pullulans* being considered.
- There is a wide range of benefits from the use of pullulans manufactured using *A. pullulans*. Pullulans is used in a wide range of products including in food, cosmetics, pharmaceuticals, electronics and biomedical applications.
- The toxicity of *A. pullulans* is very low to nil with no evidence of skin or eye irritancy. *A. pullulans* is not mutagenic, pathogenic or infective and does not produce toxins or active metabolites. *A. pullulans* is a moderate skin sensitiser (Buehler method); however there are no known reports of occupational sensitisation despite industrial and farm use.
- Risk of sensitisation to *A. pullulans* can be mitigated through personal protective equipment controlled through APVMA labelling regulations.

### ***Public submissions on the interim decision***

One (1) submission was received that supported the delegate's interim decision, due to the wide range of benefits from its use and low toxicity profile.

### ***Delegate's final decision***

The delegate notes the submission; however, as no new evidence has been received to alter the interim decision, the delegate has confirmed that the final decision and reasons for the final decision are in keeping with those for the interim decision.

The delegate's final decision is to create a new Appendix B for *Aureobasidium pullulans*. The implementation date is **1 October 2017**.

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

### 4. New Chemical Entities – medicines for human therapeutic use

#### Summary of delegate's final decisions

The implementation date of the below final decisions is **1 October 2017** unless separately specified.

Substance	Final Decision
Migalastat	<b>Schedule 4 – New Entry</b> MIGALASTAT.
Fosfomycin	<b>Schedule 4 – New Entry</b> FOSFOMYCIN.
Dupilumab	<b>Schedule 4 – New Entry</b> DUPILUMAB.
Influenza virus haemagglutinin	Influenza virus haemagglutinin does not require specific scheduling as it is captured by the Schedule 4 group entry for influenza and coryza vaccines.
Bezlotoxumab	<b>Schedule 4 – New Entry</b> BEZLOTOXUMAB.
Rurioctocog alfa pegol	Rurioctocog alfa pegol is exempt from scheduling as it falls under Appendix A – General Exemptions under HUMAN BLOOD PRODUCTS.

#### 4.1 Migalastat

##### *Scheduling proposal*

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

##### *Substance summary*

Migalastat acts as a pharmacological chaperone, binding to mutant forms of the enzyme,  $\alpha$ -galactosidase A. Through binding, migalastat stabilises  $\alpha$ -galactosidase A and allows it to be transported into lysosomes. Here,  $\alpha$ -galactosidase A is able to reduce the levels of glycosphingolipids, fatty substances that can accumulate in cells in the body including in the heart and kidneys.

Migalastat is indicated for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease ( $\alpha$ -galactosidase A deficiency) and who have an amenable mutation.

### ***Scheduling status***

Migalastat is not specifically scheduled or captured by any group entries in the current [Poisons Standard](#).

### ***International regulations***

Migalastat is authorised in the EU. Migalastat is not classified in New Zealand, Canada or the USA.

### ***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.

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 Migalastat in Schedule 4, with an implementation date of **1 October 2017**.

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

#### **Schedule 4 – New Entry**

MIGALASTAT.

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:

- Migalastat is an NCE with no marketing experience in Australia.
- The proposed indication for Migalastat is for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease ( $\alpha$ -galactosidase A deficiency) and who have an amenable mutation.
- Fabry disease is a rare disease associated with serious health risks. Treatment should be supervised by a specialist physician experienced in the diagnosis and management of Fabry disease.
- Treatment with Migalastat requires clinical evaluation and monitoring by a medical practitioner.
- Labelling needs to comply with the requirements for a prescription only medicine.

- The potential for abuse of Migalastat is low.

## 4.2 Fosfomycin

### *Scheduling proposal*

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

### *Substance summary*

The proposed indications for Fosfomycin (with trometamol) is for treatment of acute uncomplicated lower urinary tract infections, caused by pathogens sensitive to fosfomycin, in women above 12 years of age and for prophylaxis of urinary tract infections in surgical or diagnostic procedures involving the lower urinary tract in adult males and females.

Fosfomycin acts on at the first stage of bacterial wall synthesis. It inhibits the phosphoenolpyruvate transferase enzyme, thereby irreversibly blocking the condensation of uridine diphosphate-*N*-acetylglucosamine with *p*-enolpyruvate.

### *Nomenclature*

ANN/INN: fosfomycin trometamol

### *Scheduling status*

Fosfomycin is not specifically scheduled and is not captured by any entry in the current [Poisons Standard](#).

Trometamol is in Schedule 4 as follows:

#### **Schedule 4**

TROMETAMOL in preparations for injection **except** in preparations containing 3 per cent or less of trometamol.

### *International regulations*

Fosfomycin trometamol is not registered in New Zealand or Canada. In the USA, fosfomycin tromethamine is supplied in an oral suspension (sachet) dosage form to be dissolved in water and is available by prescription only.

### *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.

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 fosfomycin in Schedule 4, with an implementation date of 1 October 2017.

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

#### **Schedule 4 – New Entry**

FOSFOMYCIN.

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 an NCE with no clinical experience in Australia.
- The potential for abuse of fosfomycin is unlikely.

## **4.3 Dupilumab**

### ***Scheduling proposal***

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

### ***Substance summary***

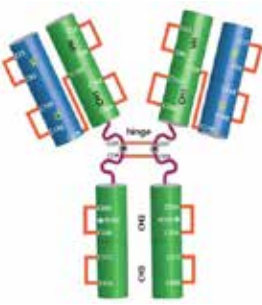
Dupilumab is an immunoglobulin G4-kappa, anti-[*Homo sapiens* IL4R (interleukin 4 receptor, IL4RA, IL-4RA, CD124)], *Homo sapiens* monoclonal antibody (mAb) produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

Dupilumab is a fully human mAb that inhibits IL-4 and IL-13 signalling by specifically binding to the IL-4R $\alpha$  subunit of the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL 4R $\alpha$ / $\gamma$ c), and both IL-4 and IL 13 signalling through the Type II receptor (IL-4R $\alpha$ /IL-13R $\alpha$ ).

Dupilumab is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical therapy.

**Table 4.3: Identifiers, properties and naming of Dupilumab**

Property	Dupilumab
CAS Number	1190264-60-8

Property	Dupilumab
Structure	
Molecular formula	$C_{6512}H_{10066}N_{1730}O_{2052}S_{46}$
Molecular weight	146.9 kDa
Other name/s	FDA UNII: 420K487FSG

### ***Scheduling status***

Dupilumab is not specifically scheduled in the current [Poisons Standard](#) but is captured by 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***

Dupilumab is unclassified in New Zealand and Canada, but it is currently under review by the FDA in the USA (Sept, 2016).

### ***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.

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 dupilumab in Schedule 4, with an implementation date of **1 October 2017**.

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

#### **Schedule 4 – New Entry**

DUPILUMAB.

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; and (c) the toxicity of a substance.

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

- Dupilumab is an NCE with no clinical experience in Australia.
- Dupilumab is intended to treat moderate to severe atopic dermatitis.
- There is potential for increased infection, possible interference with immune response to vaccines and a theoretical risk that it may increase potential for malignancy.
- The potential for abuse of dupilumab is unlikely.

## **4.4 Influenza virus haemagglutinin**

### ***Scheduling proposal***

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

### ***Substance summary***

Influenza virus haemagglutinin is a purified, inactivated influenza vaccine (surface antigen), containing the following four influenza strains recommended for the 2018 influenza season:

- A/H1N1 – like strain
- A/H3N2- like strain
- B/Victoria lineage – like strain
- B/Yamagata lineage – like strain

Influenza virus haemagglutinin is indicated for the prevention of influenza caused by influenza virus, types A and B. For full details regarding recommendations for influenza vaccination, please refer to the relevant National Immunisation Guidelines. Influenza virus haemagglutinin is indicated in adults (18 years of age and older).

### ***Scheduling status***

Influenza virus haemagglutinin is not specifically scheduled in the current [Poisons Standard](#) but is captured by the following group entry:

#### **Schedule 4**

INFLUENZA AND CORYZA VACCINES:

- a) for parenteral use; or
- b) for nasal administration.

### ***International regulations***

Influenza virus haemagglutinin is not specifically classed as a Prescription Medicine in New Zealand, Canada or the US, however, influenza vaccines are listed as Prescription Medicines in New Zealand, Schedule D – biological products in Canada, and are licensed products in the US.

### ***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's final decision is that influenza virus haemagglutinin does not require specific scheduling as it is captured by the Schedule 4 group entry for influenza and coryza vaccines.

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:

- Influenza virus haemagglutinin is a new vaccine with no clinical and marketing experience in Australia.
- Influenza virus haemagglutinin is for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine and is captured by the group entry for influenza and coryza vaccines.
- Adverse events may include sweating, pyrexia, myalgia, Headache, local injection site reactions.
- Influenza virus haemagglutinin is contraindicated in people with hypersensitivity to the active substances, to any of the excipients and to residues of eggs (ovalbumin, chicken proteins), formaldehyde, cetrimonium bromide, polysorbate 80, or gentamicin. Immunisation should be postponed in patients with febrile illness or acute infection.
- Influenza virus haemagglutinin should be administered by intramuscular or deep subcutaneous injection
- The potential for abuse of Influenza virus haemagglutinin is unlikely.

## 4.5 Bezlotoxumab

### *Scheduling proposal*

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

### *Substance summary*

Bezlotoxumab is a specific fully human monoclonal antibody that binds with high affinity to *C. difficile* toxin B. Bezlotoxumab is an IgG<sub>1</sub> immunoglobulin, produced in Chinese hamster ovary cells by recombinant DNA technology.

Bezlotoxumab is indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.

**Table 4.5: Identifiers, properties and naming of Bezlotoxumab**

Property	Bezlotoxumab
CAS Number	1246264-45-8
Molecular formula	C <sub>6464</sub> H <sub>9974</sub> N <sub>1726</sub> O <sub>2014</sub> S <sub>46</sub>
Molecular weight	148.2 kDa
ANN/INN	eBS ID: 110777
Other:	eBS ID: 110777 ATC code: J06BB21

### *Scheduling status*

Bezlotoxumab is not specifically scheduled in the current [Poisons Standard](#) but is captured by 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*

Bezlotoxumab is a Prescription Medicine in the USA but not classified in New Zealand or Canada.

### *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.

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 bezlotoxumab in [Schedule 4], with an implementation date of **1 October 2017**.

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

#### **Schedule 4 – New Entry**

##### **BEZLOTOXUMAB.**

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:

- Bezlotoxumab is an NCE with no clinical/marketing experience in Australia
- Bezlotoxumab should be prescribed by medical professionals who are familiar with the diagnosis and management of *Clostridium difficile* infection.
- The most common adverse reactions following treatment with Bezlotoxumab are nausea, diarrhoea, pyrexia and headache.
- Bezlotoxumab is a pregnancy Category B2 drug.
- The potential for abuse of bezlotoxumab is unlikely.

## **4.6 Rurioctocog alfa pegol**

### ***Scheduling proposal***

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

### ***Substance summary***

Rurioctocog alfa pegol is a full-length recombinant factor VIII conjugated to polyethylene glycol.

Rurioctocog alfa pegol is indicated in haemophilia A (congenital factor VIII deficiency) patients for:

- the control and prevention of bleeding episodes;
- routine prophylaxis to prevent or reduce the frequency of bleeding episodes; and
- perioperative management (surgical prophylaxis).

### ***Nomenclature***

ABN – Rurioctocog alfa pegol

### ***Scheduling status***

Rurioctocog alfa pegol is not specifically scheduled in the current [Poisons Standard](#). However, as a recombinant clotting factor, rurioctocog alfa pegol is exempt from scheduling as it is captured by the Appendix A entry for HUMAN BLOOD PRODUCTS, (iv) clotting factors.

### ***International regulations***

Rurioctocog alfa pegol is not specifically classified by Medsafe New Zealand, however may be captured by the entry 'Blood clotting factors' classified for general sale.

### ***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 that rurioctocog alfa pegol is exempt from scheduling as it falls under Appendix A – General Exemptions under HUMAN BLOOD PRODUCTS.

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:

- The potential for abuse of rurioctocog alfa pegol is unlikely.