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

October 2015

Notice under subsections 42ZCZP of the Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary to the Department of Health hereby gives notice of delegate's interim decisions for amending the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* - SUSMP) under subsection 42ZCZP the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect of the decision.

This notice provides the interim decisions of the delegate, the reasons for those decisions and invites further submissions for the applicant and parties who made valid submissions in response to the original invitations for submissions (published on 2 April 2015 and 11 June 2015 for general scheduling applications and for delegate-initiated scheduling application respectively at https://www.tga.gov.au/consultation-invitation/consultation-invitation-public-comment-acms-meeting-july-2015 and https://www.tga.gov.au/consultation-invitation/consultation-invitation-public-comment-acms-meeting-july-2015-0). Edited versions of these submissions are available at https://www.tga.gov.au/public-submissions-scheduling-matters.

Further submissions must be relevant to the proposed amendment, must address a matter mentioned in section 52E of the *Therapeutic Goods Act 1989.* As per subsection 42ZCZP of the Regulations, further submissions in relation to the interim decision are to be made within 10 business days after the publication of the notice and therefore, must be received by the closing date **15 October 2015**.

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

Please note that all valid submissions received on or before the closing date will be published following removal of confidential information. It is up to the person making the submissions to highlight any information which they wish to be considered as confidential. Material claimed to be commercial-in-confidence will be considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2015), issued by the National Coordinating Committee on Therapeutic Goods. The SPF is accessible at https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals.

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

Medicines.Scheduling@tga.gov.au for items referred to the Advisory Committee on Medicines Scheduling.

The closing date for further submissions is **15 October 2015**.

Glossary

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

Abbreviation	Name
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
COMB	Complementary & OTC Medicines Branch
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
DPSSC	Drugs and Poisons Schedule Standing Committee
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
GIT	Gastrointestinal tract
GP	General practitioner

Abbreviation	Name
HCN	Health Communication Network
IMAP	Inventory Multi-tiered Assessment Prioritisation
INN	International Non-proprietary Name
ISO	International Standards Organization
LC_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MDB	Medical Devices Branch (formerly Office of Devices Authorisation [ODA])
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission

Abbreviation	Name
OCM	Office of Complementary Medicines (now part of Complementary & OTC Medicines Branch [COMB])
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])
ODA	Office of Devices Authorisation (now Medical Devices Branch [MDB])
OMA	Office of Medicines Authorisation (now Prescription Medicines Authorisation Branch [PMAB], and formerly Office of Prescription and Non-prescription Medicines)
OOS	Out of session
OTC	Over-the-counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority existing chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PMAB	Prescription Medicines Authorisation Branch (formerly Office of Medicines Authorisation (OMA), and Office of Prescription and Non-prescription Medicines)
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program

Abbreviation	Name
QUM	Quality Use of Medicines
RASML	Required Advisory Statements for Medicine Labels
RFI	Restricted flow insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working party
WS	Warning statement

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Part A - Interim decisions on matters referred to an expert advisory committee

1. Scheduling proposals referred to the August 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS #15)

1.1 Codeine

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- Proposal to delete the Schedule 3 entry for codeine, and reschedule all current Schedule 3 codeine to Schedule 4 due to issues including morbidity, toxicity and dependence.
- Consideration could include whether all current Schedule 3 preparations should be rescheduled to Schedule 4, or whether any rescheduling to Schedule 4 should only apply to combination analgesic products containing codeine.
- Consideration could include whether the Schedule 2 entry for codeine should also be amended.

Substance summary

Codeine or its salts, especially the phosphate, are given orally in the form of linctuses for the relief of cough, and as tablets for the relief of mild to moderate pain, often with a non-opioid analgesic such as aspirin, ibuprofen, or paracetamol. The phosphate is also given by intra muscular injection, in doses similar to those used orally, for the relief of pain; the intravenous, subcutaneous, and rectal routes have also been used.

For the relief of pain codeine phosphate may be given in doses of 30 to 60 mg every 4 hours to a usual maximum of 240 mg daily.

To allay non-productive cough codeine phosphate may be given in doses of 15 to 30 mg three or four times daily.

Codeine phosphate is also used as tablets or in mixtures for the symptomatic relief of acute diarrhea in doses of 15 to 60 mg given three to four times daily.

Other codeine salts used include the hydrochloride, saulfate, camsilate, and hydrobromide. Codeine polistirex (a codeine and sulfonate diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparation.

Scheduling status

CODEINE is currently listed in Schedules 8, 4, 3 and 2.

SCHEDULE 8

CODEINE except when included in Schedule 2, 3 or 4.

SCHEDULE 4

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

a. in divided preparations containing 30 mg or less of codeine per dosage unit; or

b. in undivided preparations containing 1 per cent or less of codeine,

except when included in Schedule 2 or 3.

SCHEDULE 3

CODEINE when:

a. not combined with any other opiate substance;

b. compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:

   i. in divided preparations containing 12 mg or less of codeine per dosage unit; or

   ii. in undivided preparations containing 0.25 per cent or less of codeine;

c. labelled with a recommended daily dose not exceeding 100 mg of codeine; and

d. in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,

except when included in Schedule 2.

SCHEDULE 2

CODEINE in preparations for the treatment of coughs and colds when:

a. not combined with any other opiate substance;

b. compounded with one or more other therapeutically active substances, of which at least one is phenylephrine and not more than one is an analgesic substance:

   i. in divided preparations containing 10 mg or less of codeine per dosage unit; or

   ii. in undivided preparations containing 0.25 per cent or less of codeine;

c. labelled with a recommended daily dose not exceeding 60 mg of codeine; and

d. in packs containing not more than 6 days' supply at the maximum dose recommended on the label.

Scheduling history

National Drugs and Poisons Schedule Committee: June 2008

The NDPSC agreed to form a Codeine Working Party to review the availability of all OTC combination analgesics containing codeine. This followed concerns raised at previous NDPSC meetings (June 2005, October 2005 and June 2007) of abuse of codeine from a codeine-ibuprofen combination analgesic product (by cutting a bi-layer tablet in half to access the codeine, or separating codeine from the product by simple dissolution in water).

National Drugs and Poisons Schedule Committee: February 2009

The NDPSC considered a report from the Codeine Working Party, together with findings from an evaluation of OTC codeine-containing analgesics, and agreed to foreshadow a proposal to reschedule all OTC codeine to Schedule 3 (with suggestions to limit the maximum daily dose to 100 mg codeine, limit the maximum pack size to 5 days' supply, restrict divided preparations to 12 mg of codeine per dosage unit and restrict undivided preparations to 0.25% codeine). In addition, a member proposed to maintain a Schedule 2 entry for codeine + phenylephrine, if all other OTC codeine was included in Schedule 3. The NDPSC foreshadowed a proposal to include all OTC codeine (and not just analgesics) to encourage public comment.

National Drugs and Poisons Schedule Committee: June 2009

The NDPSC agreed that the current scheduling of OTC codeine combinations for coughs and colds remained appropriate (but with a pack size limit of 5 days' supply), and that all OTC combination analgesics containing codeine should be rescheduled from Schedule 2 to Schedule 3 (with the maximum daily dose limited to 100 mg, the duration of treatment limited to 5 days, divided preparations restricted to 12 mg of codeine per dosage unit and undivided preparations restricted to 0.25% codeine) and that Schedule 3 codeine should not be included in Appendix H. The implementation date was to be 1 May 2010.

National Drugs and Poisons Schedule Committee: October 2009

Following consideration of June 2009 post-meeting submissions and further discussion, the NDPSC agreed to amend the pack size limit for Schedule 2 cough and cold preparations to a maximum of 6 days' supply. The NDPSC also confirmed the June 2009 resolution regarding the Schedule 3 entry for all OTC combination analgesics containing codeine. The implementation date remained as 1 May 2010. An editorial amendment was made to the Schedule 3 entry at the February 2010 NDPSC meeting.

Delegates Final Decision: September 2011 - Advisory Committee on Medicines Scheduling: July 2011

The scheduling of codeine was considered as a part of the cold and cough preparation review, which looked at the use of these preparations for the treatment of children aged 2 to 12 years. Taking into consideration the committee's recommendation, the delegate decided that there should be no change to the scheduling of codeine in cold and cough preparations.

Pre-meeting public submissions

60 submissions were received.

29 submissions supported. Main Points:

- Reduce the potential for harm – particularly in paracetamol/ibuprofen products (complications due to overdose);
- Reduce the potential for abuse;
- Prevent ease of access to an opioid, meaning patients seek other low risk medications/further medical advice;
- Numerous studies/clinical evidence shows misuse/abuse and significant risk to public health;
- Not currently possible for pharmacists to monitor and control safe use of low dose codeine.
- Low dose codeine not efficacious.

25 submissions opposed. Main Points:

- Increase in bookings to see GP – cost prohibitive.
- Unable to see GP on demand – potential increase at hospital emergency departments.
- Issue for those in rural areas being able to access medication if it becomes S4.
- Increase price of medication containing codeine.
- Prefer a national, real time monitoring system.
- Lower quality of life for those with chronic pain.
- Research suggests codeine is affective for acute pain which meets the claim of short term relief.

- In 2010, the NDPSC found the S2 entry for codeine appropriate.

6 submissions did not state whether they supported the proposal or not.

ACMS advice to the delegate

The ACMS recommended the deletion of the current Schedule 2 and 3 entries for codeine and amendment of the current Schedule 4 and 8 entries to reflect this change.

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

- Risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.
- OTC intended for management of acute self-limiting pain, however, there is inappropriate use for chronic pain.
- Purpose is questioned since benefit is low.
- OTC sales data are incomplete.
- Codeine shares the properties of other opioid analgesics and is potentially capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.
- Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence.
- Increasing amount of evidence for harm from abuse.
- Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression.
- Genetic influence on codeine's action complicates risk and benefit decisions, and leads to questions regarding the role of codeine in clinical practice.
- To adequately determine the clinical needs an appropriately qualified practitioner to assess risk.

The ACMS recommended an implementation date of 1 June 2016.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- The evaluation report (not publically available);
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors[1];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to delete the current Schedule 2 and 3 entries for codeine and amend the current Schedule 4 and 8 entries to reflect this change.

The proposed implementation date is 1 June 2016. This date will allow time for education of consumers, pharmacists and medical practitioners regarding pain management and alternative analgesia available. It is noted that comments made during the Interim decision consultation period will be taken into consideration in any final decision on implementation date.

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

- Risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.
- The risk/benefit profile for codeine in doses of 8mg – 15mg per dosing unit in combination with other analgesics is unfavourable. There is also a lack of evidence of any benefit of codeine over placebo in the relief of cough, making the risk/benefit profile for this indication unfavourable also. Codeine demonstrates marked variability in its transformation to morphine in different individuals, with the potential for very severe toxicity in ultra-rapid metabolisers.
- OTC intended for management of acute self-limiting pain, however, there is inappropriate use for chronic pain.
- Purpose is questioned since benefit is low.
- The purposes for which codeine is intended to be used are for Schedule 2 products for the "treatment of coughs and colds" and for Schedule 3 products for the "temporary relief of strong pain and discomfort associated with a number of different medical conditions."
- Codeine shares the properties of other opioid analgesics and is potentially capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.
- Codeine, as a prodrug, causes its direct toxicity primarily through its biotransformation into morphine. The metabolic polymorphism discussed above leads to major variability within the population in terms of the extent and rapidity of this conversion to morphine. Ultra-rapid metabolisers, who have an accelerated rate and higher extent of conversion, are exposed to morphine concentrations that are many-fold higher than those reached in poor metabolisers. This variant is found in up to 10% of Caucasians, and higher proportions of populations of North African, Oceanic and Middle Eastern origin. Very few individuals are aware of their own metaboliser status, and it would thus be very difficult to protect ultra-rapid metabolisers by way of warnings. High concentrations of morphine in the plasma can lead to serious sedation and respiratory depression, and potentially to death.
- The potential for severe adverse effects at "usual" doses in ultra-rapid metabolisers is such that codeine appears to be an unsuitable candidate for OTC availability, with either S2 or S3 scheduling.

[1] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

This conclusion applies equally well to the products intended for treating coughs and colds, and those intended for the treatment of pain.

- Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence.
- Current labelling and packaging include insufficient warnings, and that there should be clear warning labels stating the risks of addiction and dependence, the risks of harm from the paracetamol or ibuprofen, and the risk of death. Access to codeine in Australia is inconsistent, in that the total amount of codeine available in a pack of Panadeine Extra ® (40 tablets containing 15mg each) is the same quantity as that available in a pack of codeine phosphate (20 tablets containing 30mg each), which is included in Schedule 8 and recognised to have potential for abuse or addiction.
- Some sources, including the Panadeine ® product information, suggest or imply that before taking codeine a person should know their CYP4502D6 status, and this in turn means that no person should be able to self-administer codeine that has been obtained OTC. It is argued that the benefit of medical supervision that would be obtained with a rescheduling to S4 includes the ability of the prescriber to discuss with the patient the risks of excessive opiate effect, and provide advice about actions to take if this occurs. This argument applies equally well to products currently available in both S2 and S3.
- Increasing amount of evidence for harm from abuse.
- Codeine is emerging as an increasingly commonly used drug of abuse internationally and in Australia. Data from the national opioid pharmacotherapy statistics in 2013 showed that codeine was the opioid drug of dependence for 1,038 clients receiving opioid substitution pharmacotherapy. The actual number was likely to be higher than this because of missing data. Another recently published study of 902 people who inject illicit drugs found that about one third had misused OTC codeine during the preceding six months.
- Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression.
- Genetic influence on codeine's action complicates risk and benefit decisions, and leads to questions regarding the role of codeine in clinical practice.
- An appropriately qualified practitioner needs to assess the risk before making the decision that codeine will be used.
- A recently released combination of two non-opioid analgesics (ibuprofen plus paracetamol) appears to be more effective than the CCAs, with a number needed to treat (NNT) of 1.5. This combination would fill any gap left by the unavailability of CCAs over the counter, giving consumers access to a more effective analgesic without requiring a prescription and without the risks of the marked variability in pharmacokinetics or abuse potential that are associated with codeine.
- Potential unintended consequences and disadvantages of a decision to reschedule CCAs to S4 need to be considered. One would be a reduction in the availability of analgesics for moderate to severe pain, although the evidence suggests that the addition of codeine adds only a minor additional analgesic effect over and above that of the ibuprofen or paracetamol in the combination product. The recent introduction of a paracetamol/ibuprofen combination may fill this niche more effectively than the CCAs have done, without the disadvantages of codeine. A reduction in the availability of a drug known as an anti-tussive agent, despite the lack of evidence available to support this, would also occur, but significant actual disadvantages are unlikely to occur. No other potential disadvantages to the community are readily identified.
- The major impact on public health of the proposed amendment would be a reduction in the risk to those individuals who, unbeknownst to themselves, have a rapid metaboliser phenotype of

CYP4502D6 and are therefore at significant risk of excessive morphine concentrations following ingestion of usually recommended doses of codeine for any indication.

- Codeine is an opioid which must be metabolised by CYP2D6 to its active metabolite, morphine, for its analgesic effect. Different genetic groups show significant variations in metabolism of codeine. Of particular concern are "ultra-rapid" metabolisers, where the accelerated metabolism of codeine to morphine results in an increased risk of morphine toxicity and adverse events.
- The function of the enzyme carrying out that transformation is genetically controlled and highly variable between individuals because of the existence of multiple forms of the relevant gene; the difference in exposure to morphine following a standard dose of codeine can be up to 45-fold higher in ultra-rapid metabolisers compared with poor metabolisers.
- Ultra-rapid metabolisers are therefore at risk of morphine overdose, with potentially fatal consequences, following "usual" doses of codeine.
- Individuals rarely know their metaboliser status, and testing is not readily available.
- All other opioids are at least Schedule 4.
- The approved indication for the S3 codeine products is for the "temporary relief of strong pain and discomfort associated with a number of different medical conditions". It is noted that there is significant use of S3 codeine products for longer term relief of chronic pain and a number of public submissions by consumers have noted that this is how they use it.
- The management of chronic pain would be better achieved by having medical practitioner input with appropriate advice on non-medicine treatments and appropriate medicinal treatment for the chronic pain, rather than self-treating with long term codeine containing analgesics (CCAs).
- The presence of codeine in OTC combination analgesics contributes to severe adverse outcomes associated with overdosage of the paracetamol or ibuprofen component, because the development of dependence on codeine leads to overuse of the combination. Anecdotally some abusers of OTC codeine products are consuming 30 to 70 tablets/capsules per day of the CCAs.
- In Europe codeine is not an OTC medicine (i.e. is a prescription only medicine at least) in 13 countries being Austria, Belgium, Croatia, the Czech Republic, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Slovakia, Spain and Sweden.
- Codeine is also a Prescription Medicine in the USA, Hong Kong, Iceland, India, Japan, the Maldives, Romania, Russia, and the United Arab Emirates.
- There is no evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen.
- In February 2009 NDPSC decided that:
  - Based on the currently available information from Australia, the evaluator concluded that there was potential for significant harm from OTC combination analgesics containing codeine (CACC) and even death, and it was not possible to accurately estimate the associated risk, although the following were reasonably assumed:
    - the proportion of all users that abuse OTC CACC is low.
    - the risk of harm among all users of OTC CACC is low.
    - the risk of harm among abusers of OTC CACC is high.
  - Central consideration in allowing OTC supply of codeine combinations was that the benefits outweighed the risks and therefore asserted that the insufficient data on efficacy may mean that the benefits no longer outweighed the risks. While agreeing that efficacy remains important to

any case justifying OTC supply of codeine, the Committee noted the Codeine Working Party advice that there was not sufficient information available to the Members at this time to resolve the question of codeine efficacy at ≤ 30mg.

- The NDPSC rescheduled OTC codeine-containing combination analgesics to Schedule 3 in 2010, with the aim of increasing surveillance of codeine medication usage by pharmacists to ensure quality use of medicines, as it was recognised that there is a potential for harm if used inappropriately. The Schedule 3 entry included limits on the maximum daily dose and pack size, and restrictions on the quantities of codeine in divided (and undivided) preparations.
- Rescheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals. Since the rescheduling of codeine from 2010 there hasn't been the reduction in risk that might have occurred.
- Codeine is increasingly a drug of abuse in Australia, and some individuals have developed severe adverse effects from the high doses of paracetamol and ibuprofen that accompany the use of large numbers of tablets in a codeine-dependent person. A pack of CCA available under S3 contains the same total dose of codeine as a pack of codeine available only under S8.
- Since OTC CCAs were rescheduled to Schedule 3 in 2010, industry and pharmacy organisations have not been able to fully address concerns regarding codeine dependence.
- Codeine in the unit doses present in OTC products provides very little additional analgesic effect over and above that provided by the accompanying drug in the combination. It is also noted that there are new combination products with paracetamol and ibuprofen which are more efficacious than low dose CCAs.
- CCAs do not meet the criteria required for Schedule 3, particularly that they are not "substantially safe in use but require professional advice or counselling by a pharmacist", and cannot be said to "not require close medical management." Rather, it would be more appropriate for CCAs to be prescribed so that consumers can be warned about the potential risks and adverse effects can be more closely monitored.
- Concurrently the Advisory Committee on the Safety of Medicines (ACSOM) has recently considered the risks of codeine use in children, and codeine use in persons who are ultra-rapid metabolisers of codeine. Excerpts from the meeting statement from ACSOM 28 state:
  - ACSOM agreed that the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years.
  - As it is not possible to identify in advance the subgroup of children who are at increased risk of toxicity (e.g. through being an ultra- rapid metaboliser), the committee's advice relates to the risks for all children under the age of 12.
  - ACSOM also agreed that the risks associated with codeine outweigh the benefits of codeine for analgesia in children under the age of 18 years who have undergone tonsillectomy or adenoidectomy for sleep apnoea, for the same reasons as for children under the age of 12 years, as above. This is consistent with the United States Food and Drug Administration (US FDA) position that codeine use after adenotonsillectomy is contraindicated. The committee also noted that there have been a number of adverse event cases observed that are not clearly explained but may relate to sleep apnoea.
  - ACSOM also agreed that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers.

- As a mother's knowledge of her own experience with codeine (and indirectly, metaboliser status) does not predict the infant's response, breastfeeding should be a contraindication for codeine.
- ACSOM noted the following contraindications which were recommended in the TGA's safety review to be included in the codeine Product Information - use in children under the age of 12 for any reason; use in people of any age known to be ultra-rapid metabolisers; use in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea; and use by breastfeeding mothers.
- The committee noted that the OTC availability of codeine-containing medicines supported a general perception in the community that codeine is safe. Therefore, communication of the contraindications by label changes alone was not likely to achieve the desired outcome of risk reduction. Additional measures including education and the possible rescheduling of codeine-containing medicines also needed to be considered. The committee supported consistency and harmonisation in labelling across all codeine-containing medicines, especially regarding advice to breastfeeding mothers.
- Activities to reduce the use of codeine cannot occur in isolation from consideration of alternative pain management strategies. Pain management strategies that do not include codeine needed to be carefully defined and their implementation carefully considered. For example, direct administration of morphine could be considered as an alternative and the issues of analgesic polypharmacy and escalation up the 'pain ladder' also require consideration in the development of any pain management strategies that omit codeine.

- It should be noted that the following factors for a Schedule 3 medicine in the Scheduling Policy Framework (SPF) are not met:
  - Codeine does not meet the SPF scheduling factors for inclusion in Schedule 3. In particular, criterion 2 is not satisfied – i.e. "The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by a pharmacist."
- Codeine containing analgesics should now be included in Schedule 4 because codeine meets the factors in the Scheduling Policy Framework required for Schedule 4, and particularly the following factors:
  - In particular, use at established therapeutic dosage levels may produce dependency (criterion 3).
  - Codeine also meets SPF Schedule 4 criterion 1 (diagnosis, management or monitoring of chronic pain conditions requires medical or dental intervention before use and, although OTC codeine products are intended for short-term use, many consumers use them for chronic pain without medical intervention) and criterion 7 (its use has contributed to, or is likely to contribute to, communal harm).
- Other issues:
  - Codeine alone is ineffective as an analgesic in doses <60mg (number needed to treat (NNT) to achieve one patient obtaining a 50% pain relief response is 12).
  - Compound analgesics containing codeine plus paracetamol or codeine plus ibuprofen, show minimal analgesic benefit compared to the simple analgesics (paracetamol or ibuprofen) alone.
  - In up to 10% of the population (poor metabolisers), it is ineffective but can still cause harmful effects.
  - In up to 4-10% of the population (ultra-rapid metabolisers), it can cause life threatening toxicity.

  - If codeine is to remain in use as an analgesic, then the patient's metaboliser status needs to be ascertained prior to prescription or dispensing, however this is not practical.

- It was suggested that there were options to try and minimise the abuse related to CCAs by either expanding Project Stop or real-time monitoring of CCA use.
- Project Stop relates to the monitoring of sales of pseudoephedrine and is a police related activity to prevent diversion of pseudoephedrine as a precursor for illegal methamphetamine manufacture.
- The Project Stop website states its role as:
  - Project STOP is an initiative of the Pharmacy Guild of Australia to address the problem of precursor diversion through Australian Community Pharmacies. The most common precursor sourced through the community pharmacy channel is Pseudoephedrine which can be used in the illegal manufacture of methamphetamines.
  - Project STOP is an online tool which provides decision support to pharmacists who need to establish whether requests for products containing Pseudoephedrine are legitimate. It also assists pharmacists in meeting their state regulatory recording requirements where they exist.
- Despite the risks of abuse identified when CCAs were up-scheduled in 2010 there has been no initiative to include CCAs into Project Stop prior to the application to up-schedule codeine to S4.
- Real-time monitoring of medicines is not currently in place in any jurisdiction other than Tasmania where it is restricted to S8 medicines. There is no formal implementation of real-time monitoring across Australia and whether its implementation would it is unsure whether it would ever come down to S3 medicines.
- In both Project Stop and real-time monitoring the onus on prevention of supplying CCAs would fall on pharmacists when dealing directly with consumers.
- Another option considered was decreasing the pack size of CCAs from the current limit of five days with a recommended daily dose not exceeding 100 mg of codeine to a pack size limit of three days' supply as has occurred in the United Kingdom. However decreasing the available pack sizes of OTC codeine products might help reduce the incidence of new users becoming dependent on codeine, but is unlikely to be effective for those who are already dependent.
- A number of the pre-meeting submissions considered it unduly burdensome to require consumers to obtain a prescription for supply of codeine combination analgesics. However, pharmacists can recommend alternate pain relief products, such as a paracetamol-ibuprofen combination, or consumers could obtain a prescription (to have on hand when needed for acute pain) if they visit a general practitioner for any reason.
- To be consistent with the interim decision to remove the S3 entry for codeine and for the issues around codeine in the 12 and under population as recommended by ACSOM the S2 entry should also be deleted.
- There are alternative OTC analgesic products for short-term pain relief.
- The ACMS recommendation and reasons.

Schedule entry

SCHEDULE 8 – AMENDMENT

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

SCHEDULE 4 – AMENDMENT

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

a) in divided preparations containing 30 mg or less of codeine per dosage unit; or a

b) in undivided preparations containing 1 per cent or less of codeine.

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

SCHEDULE 3 – DELETE ENTRY

~~CODEINE when:~~
~~a) not combined with any other opiate substance;~~
~~b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:~~
~~i) in divided preparations containing 12 mg or less of codeine per dosage unit; or~~
~~ii) in undivided preparations containing 0.25 per cent or less of codeine;~~
~~c) labelled with a recommended daily dose not exceeding 100 mg of codeine; and~~
~~d) in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,~~
~~**except** when included in Schedule 2.~~

SCHEDULE 2 – DELETE ENTRY

~~CODEINE in preparations for the treatment of coughs and colds when:~~
~~a) not combined with any other opiate substance;~~
~~b) compounded with one or more other therapeutically active substances, of which at least one is phenylephrine and not more than one is an analgesic substance:~~
~~i) in divided preparations containing 10 mg or less of codeine per dosage unit; or~~
~~ii) in undivided preparations containing 0.25 per cent or less of codeine;~~
~~c) labelled with a recommended daily dose not exceeding 60 mg of codeine; and~~
~~d) in packs containing not more than 6 days' supply at the maximum dose recommended on the label.~~

1.2 Naloxone

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To create a new Schedule 3 entry for naloxone when in single use prefilled syringe preparations for injection containing 400 µg/mL of naloxone or less.

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

Substance summary

Naloxone is a specific opioid antagonist that acts competitively at opioid receptors. It is an antagonist of opioids that possesses agonist or mixed agonist-antagonist activity, although larger doses may be needed for compounds with the latter activity. Naloxone is used to reverse opioid central depression, including respiratory depression, induced by natural or synthetic opioids, in the management of known or suspected opioid overdosage, postoperatively after the use of opioids during surgery, and in neonates when opioid analgesics have been given to the mother during labour.

Naloxone hydrochloride is usually given intravenously for the most rapid action, with onset within two minutes. The onset of action is only slightly less rapid when it is given intramuscularly or subcutaneously. Other routes of administration, including endotracheal, have also been used. The

duration of action of naloxone is dependent on the dose and route, but is generally in the range of 1 to 4 hours. An intravenous infusion may be used for a sustained response; commonly, 2 mg of naloxone hydrochloride is added to 500 mL of sodium chloride 0.9% or glucose 5% to obtain a concentration of 4 micrograms/mL.

In the management of known or suspected opioid overdosage, the initial dose of naloxone hydrochloride is 0.4 to 2 mg given intravenously and repeated if necessary at intervals of 2 to 3 minutes. If no response has been seen after a total dose of 10 mg then the diagnosis of overdosage with drugs other than opioids should be considered. If the intravenous route is not feasible the intramuscular or subcutaneous route can be used. When sustained opioid antagonism is needed, an intravenous infusion may be used. Dosage regimens have not been well established, and the rate of infusion must be titrated according to the patient's response.

Some have recommended an infusion of 60% of the initial dose per hour given via an infusion pump, either undiluted, or diluted to a concentration of 200 micrograms/mL in glucose. Others have suggested an initial intravenous loading dose of 400 micrograms, followed by a continuous infusion at an initial rate of 400 micrograms/hour. Alternatively, an intravenous loading dose of 5 micrograms/kg has been suggested, followed by a continuous infusion of 2.5 micrograms/kg per hour.

Scheduling status

Naloxone is currently listed in Schedule 4.

Scheduling history

National Health and Medical Research Council – Poisons Scheduling Sub-committee: March 1973

The committee recommended that the Schedule 4 entry for Morphine antagonists should be amended to include naloxone, and that the Schedule 8 entry for Oxymorphone should be amended to specify "Oxymorphone except when included in Schedule 4" (as naloxone and some other morphine antagonists were derivatives of oxymorphone).

National Health and Medical Research Council – Poisons Scheduling Sub-committee: August 1985

The committee decided to delete the general Schedule 4 entry for Morphine antagonists, and create a new Schedule 4 entry for Naloxone.

Pre-meeting public submissions

96 individual submissions were received (57 as a part of a campaign by the Sydney Medically Supervised Injecting Centre).

All submissions supported the proposal to down-schedule naloxone in single use pre-filled syringes for injections to Schedule 3. Main points:

- Schedule 3 entry will remove barriers to access;
- Naloxone is safe and has no effect on anyone without opioids in their system;
- Low to no abuse potential.

One submission, while supporting down-scheduling of naloxone, did not support the wording of the proposal. This submission suggested new wording to restrict Schedule 3 listing to a single dose form:

- To amend the scheduling of naloxone to include single doses containing 2 mg or less and a recommended total dose of 10 mg or less.

ACMS advice to the delegate

The ACMS recommended a new Schedule 3 entry for naloxone when packaged and labelled for the treatment of opioid overdose.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: a) the risks and benefits of the use of the substance; b) the purposes for which a substance is to be used and the extent of use 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 recommendation comprised the following:

- Naloxone is a well-tolerated life-saving medicine with minimal side effects.
- The benefits of increasing availability of naloxone outweigh the risks.
- Naloxone is used as an antidote to opioid overdose.
- The dose form, labelling and packaging of Schedule 3 naloxone must be made suitable for consumer use.
- Naloxone does not replace other resuscitation treatments and procedures.

ACMS recommended an implementation date of 1 February 2016.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[2];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 3 entry for naloxone when used for the treatment of opioid overdose be created.

The proposed implementation date for the new Schedule 3 entry is 1 February 2016.

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

[2] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

The reasons for the decision comprised the following:

- Naloxone is a well-tolerated life-saving medicine with minimal side effects. The benefits outweigh the risks.
- Naloxone is used as an antidote to opioid overdose. The dose form, labelling and packaging of Schedule 3 naloxone must be made suitable for consumer use. Naloxone does not replace other resuscitation treatments and procedures.
- International experience and the outcomes of a trial conducted in the Australian Capital Territory (ACT) support the view that easier availability of naloxone is likely to decrease the proportion of opioid overdoses which result in death.
- Benefits of rescheduling naloxone for reversal of opioid overdose to Schedule 3 include that products would be supplied labelled with full and clear instructions for use, understandable by consumers. People who need naloxone would be able to obtain it more easily, which is likely to decrease the proportion of (deliberate or accidental, usually illicitly obtained) opioid overdoses that result in death. Increased accessibility would also potentially reduce morbidity due to opioid overdose, such as hypoxic brain damage.
- Risks of rescheduling include an incentive for supply when not necessary, that opioid users may use opioids in a riskier manner knowing that an antidote is available (although there is no evidence that this is the case), that bystanders may be less likely to call an ambulance, and risks of unsafe administration.
- However, there are few inherent risks with use of naloxone. There is no risk of abuse of naloxone itself. Adverse events are rare, there are no major adverse effects if naloxone is given wrongly or not absorbed, and naloxone has no effect in the absence of an opioid.

Schedule entry

SCHEDULE 3 – NEW ENTRY

NALOXONE when used for the treatment of opioid overdose.

SCHEDULE 4 – AMENDMENT

NALOXONE except when in Schedule 3.

1.3 Orlistat

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To amend the scheduling of orlistat to down-schedule oral preparations for weight control purposes containing 120 mg or less of orlistat per dosage unit from Schedule 3 to Schedule 2.

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

Substance summary

Orlistat is a gastric and pancreatic lipase inhibitor that limits the absorption of dietary fat. It is used together with dietary modification in the management of obesity, i.e. in patients with a BMI of 30 kg/m2 or greater. It may also be used in overweight patients with a BMI of 27 kg/m2 or more, if there are associated risk factors. Orlistat is given orally in a usual dose of 120 mg three times daily, immediately before, during, or up to 1 hour after meals. The patient's diet should be reduced in calories and nutritionally balanced with 30% of calories obtained from fat, and the daily intake of the

major nutrients spread over the three main meals. If a meal is missed or contains no fat, the dose should be omitted. Orlistat may also be used at a lower dose of 60 mg three times daily by the same patient group.

Scheduling status

Orlistat is currently listed in Schedules 3 and 4.

SCHEDULE 3

ORLISTAT in oral preparations for weight control purposes containing 120 mg or less of orlistat per dosage unit.

SCHEDULE 4

ORLISTAT except when included in Schedule 3.

Scheduling history

National Drugs and Poisons Schedule Committee: August 1999

The NDPSC recommended that orlistat should be included in Schedule 4.

National Drugs and Poisons Schedule Committee: June 2002

The NDPSC considered an application to reschedule orlistat for the treatment of obesity from Schedule 4 to Schedule 3. At that time, the NDPSC decided that the existing scheduling of orlistat (Schedule 4) remained appropriate.

National Drugs and Poisons Schedule Committee: February 2003

The NDPSC considered a further application to reschedule orlistat for the treatment of obesity from Schedule 4 to Schedule 3. The NDPSC decided that the application did not resolve the concerns raised at the June 2002 meeting, and reconfirmed the inclusion of orlistat in Schedule 4.

National Drugs and Poisons Schedule Committee: October 2003

The NDPSC recommended inclusion in Schedule 3 of orlistat in oral preparations for weight control purposes containing 120 mg or less of orlistat. The NDPSC's decision was made on the following grounds: Safety profile of orlistat based on the low incidence of adverse effects; Orlistat was reasonably efficacious for gradual and long term weight loss when used in conjunction with exercise and dietary restriction; Obesity is a disease which can be easily recognised by consumers; Pharmacists in Australia have good training and experience in providing advice and consultation in relation to management of weight loss and treatment of obesity; and Orlistat for use in weight loss has low potential for abuse or overdose.

Pre-meeting public submissions

Five submissions were received.

Two submissions supported the proposal to down-schedule orlistat in oral preparations for weight control purposes containing 120 mg or less of orlistat per dosage unit from Schedule 3 to Schedule 2.

Main points:

- Ease supply restriction; and
- Safe medicine to use.

Three submissions opposed the rescheduling of orlistat.

Main point:

- Potential for abuse.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of orlistat remains appropriate.

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

The reasons for the recommendation comprised the following:

- Risks include decreased absorption of fat-soluble vitamins; some drug interactions; renal failure.
- Orlistat is used for the management of obesity.
- Orlistat has minimal toxicity, due to minimal absorption from oral administration.
- However, risks of rescheduling include the potential for misuse, decreased absorption of fat-soluble vitamins, some drug interactions and renal failure.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[3];
- Other relevant information.

Delegate's interim decision

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

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

The reasons for the decision comprised the following:

- Rescheduling orlistat to Schedule 2 is inconsistent with the Scheduling Policy Framework (SPF) criterion for Schedule 2 that use is substantially safe for short-term treatment.
- Orlistat has minimal toxicity, due to minimal absorption from oral administration.
- However, there is a risk of misuse if orlistat is down-scheduled to Schedule 2 as professional advice is required to ensure appropriate use of over-the-counter (OTC) orlistat. Inclusion in Schedule 2

[3] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

could increase the potential for inappropriate use or misuse of orlistat by people with anorexia, bulimia or other mental health issues.

- There are also concerns that advertising of orlistat (if included in Schedule 2) may encourage misuse or inappropriate use.
- There are risks of decreased absorption of fat-soluble vitamins, some drug interactions and renal failure.

1.4 Hydrocortisone

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To amend the scheduling of hydrocortisone and hydrocortisone acetate to include preparations for dermal human therapeutic use containing 1% or less of hydrocortisone when combined with an antifungal substance (and no other therapeutically active substance) in Schedule 2 under the following conditions:
  - in packs containing 15 g or less; and
  - for the treatment of tinea (tinea pedis, tinea cruris, tinea corporis) and other fungal skin infections; and
  - not labelled for the treatment of children under 12 years.

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

Substance summary

Hydrocortisone is a corticosteroid with both glucocorticoid and to a lesser extent mineralocorticoid activity. Hydrocortisone is used, usually with a more potent mineralocorticoid, for replacement therapy in adrenocortical insufficiency. It may also be used for its glucocorticoid properties in other conditions for which corticosteroid therapy is indicated but drugs with fewer mineralocorticoid effects tend to be preferred for the long-term systemic therapy of auto-immune and inflammatory disease. Hydrocortisone and its esters (including hydrocortisone acetate) may be used in creams, ointments or lotions, at concentrations ranging from 0.1 to 2.5%, for topical application in the treatment of skin disorders.

A number of antifungal agents are scheduled as OTC medicines for the topical treatment of fungal skin diseases (e.g. bifonazole, clotrimazole, econazole, ketoconazole, miconazole, terbinafine).

Scheduling status

Hydrocortisone is currently listed in Schedules 2, 3 and 4, and Appendix F.

Hydrocortisone acetate is currently listed in Schedules 2 and 3.

SCHEDULE 2

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use containing 0.5 per cent or less of hydrocortisone:

(a) for dermal use, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or

(b) for rectal use when combined with a local anaesthetic substance but no other therapeutically active constituent except unscheduled astringents:

(i) in undivided preparations in packs of 35 g or less; or

(ii) in packs containing 12 or less suppositories.

SCHEDULE 3

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use containing 1 per cent or less of hydrocortisone:

(a) for dermal use, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or

(b) for rectal use when combined with a local anaesthetic substance but no other therapeutically active constituent except unscheduled astringents:

(i) in undivided preparations in packs of 35 g or less; or

(ii) in packs containing 12 or less suppositories,

except when included in Schedule 2.

SCHEDULE 4

HYDROCORTISONE:

(a) for human use except when included in Schedule 2 or 3; or

(b) for the treatment of animals.

Scheduling history

National Drugs and Poisons Scheduling Committee: February 1999

The NDPSC agreed to include hydrocortisone in Schedule 2 in dermal preparations containing 0.5% or less of hydrocortisone in packs containing 30 g or less, and containing no other active ingredient or an antifungal as the only other active constituent. The NDPSC also amended the Schedule 3 entry to include dermal preparations containing 1% or less of hydrocortisone in packs containing 30 g or less, and containing no other active ingredient or an antifungal as the only other active constituent (except when included in Schedule 2).

National Drugs and Poisons Scheduling Committee: February 2007

The NDPSC agreed to amend the scheduling of preparations containing 0.5% of hydrocortisone in combination with an anaesthetic for rectal use from Schedule 3 to Schedule 2. The NDPSC noted that this would also harmonise scheduling of the substances with New Zealand. Editorial amendments were made in June and October 2007, to limit the Schedule 2 and 3 entries to human use only.

Advisory Committee on Medicines Scheduling: March 2013

The ACMS considered an application to down-schedule hydrocortisone and hydrocortisone in preparations containing 1% or less of hydrocortisone when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2. The ACMS advised the delegate that the current scheduling remained appropriate.

Pre-meeting public submissions

Five submissions were received.

Three submissions supported the rescheduling proposal.

Main point:

- Ease restrictions.

Two submissions opposed the rescheduling proposal.

Main points:

- Current scheduling is appropriate
- Potential for inappropriate consumer self-treatment of skin conditions caused by an underlying contraindicated condition.

ACMS advice to the delegate

The ACMS recommended that hydrocortisone 1% when combined with antifungal substances for dermal use in packs containing 15 g or less be down scheduled from Schedule 3 to Schedule 2 – specifically, hydrocortisone and hydrocortisone acetate should be included in Schedule 2 in preparations for dermal use containing 1% or less of hydrocortisone when combined with an antifungal substance (and no other therapeutically active substance), under the following conditions:

- in packs containing 15 g or less; and
- for the treatment of tinea (tinea pedis, tinea cruris, tinea corporis) and fungal skin infections; and
- not labelled for the treatment of children under 12 years.

The ACMS recommended an implementation date of 1 February 2016.

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

- Hydrocortisone 1% is more effective than 0.5% and the overall adverse reports are similar. The 1% strength does not produce more severe adverse reactions.
- Tinea and fungal infections are common. Itching and inflammation may occur with these infections.
- The overall risk of adverse events from topical hydrocortisone use is very small and the relative risk between the 0.5% and 1% strengths are hardly distinguishable. It has a good safety profile in short term dermal use.
- The proposed 15 g pack size minimises duration of use and the proposed labelling reduces the risk of inappropriate use.
- Providing easier access to a more effective product may be beneficial for consumers.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors [4]
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that hydrocortisone 1% when combined with antifungal substances for dermal use in packs containing 15 g or less be down scheduled from Schedule 3 to Schedule 2 – specifically, hydrocortisone and hydrocortisone acetate should be included in Schedule 2 in preparations for dermal use containing 1% or less of hydrocortisone when combined with an antifungal substance (and no other therapeutically active substance), under the following conditions:

- in packs containing 15 g or less; and
- for the treatment of tinea (tinea pedis, tinea cruris, tinea corporis) and other fungal skin infections; and
- not labelled for the treatment of children under 12 years.

The ACMS recommended an implementation date for the Schedule 2 amendment of 1 February 2016.

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

- Hydrocortisone 1% is more effective than 0.5% and the overall adverse reports are similar. The 1% strength does not produce more severe adverse reactions.
- Tinea and fungal infections are common. Itching and inflammation may occur with these infections.
- The overall risk of adverse events from topical hydrocortisone use is very small and the relative risk between the 0.5% and 1% strengths are hardly distinguishable. It has a good safety profile in short term dermal use.
- The proposed 15 g pack size minimises duration of use and the proposed labelling reduces the risk of inappropriate use.
- Providing easier access to a more effective product may be beneficial for consumers.

Schedule entry

SCHEDULE 2 – AMENDMENT

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use:

(a) for dermal use in preparations containing 0.5 per cent or less of hydrocortisone, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or

(b) for dermal use in preparations containing 1 per cent or less of hydrocortisone, in packs containing 15 g or less of such preparations, containing an antifungal substance and no other therapeutically active constituent:

[4] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

(i) for the treatment of tinea (tinea pedis, tinea cruris, tinea corporis) and other fungal skin infections; and

(ii) not labelled for the treatment of children under 12 years of age; or

(c) for rectal use in preparations containing 0.5 per cent or less of hydrocortisone, when combined with a local anaesthetic substance but no other therapeutically active constituent except unscheduled astringents:

(i) in undivided preparations in packs of 35 g or less; or

(ii) in packs containing 12 or less suppositories.

1.5 2-Hydroxyethyl methacrylate

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- Noting the Chemical Delegate's interim decision to create a new Schedule 5 entry, 2-hydroxyethyl methacrylate except when in nail preparations labelled "Avoid contact with skin", should therapeutic and/or dental use of this substance be exempt from scheduling or have a cut-off of strength? If a cut-off of strength is to be applied, is the previously proposed implementation date of 1 February 2016 appropriate for therapeutic and/or dental use?

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

Substance summary

2-Hydroxyethyl methacrylate is a methacrylate ester. It is used in cosmetic products (including in artificial nail builders, in finger paints and as a film-forming agent) and in domestic products (e.g. adhesives and sealants; paint, thinners and paint removers; washing and cleaning products; anti-freeze products). Uses at concentrations up to 10% in cosmetic products and up to 80% in domestic products have been identified in Australia. The substance also has commercial, site-limited and non-industrial uses. The main toxicity concerns relate to skin sensitisation potential, eye irritation and skin irritation. Please refer to the NICNAS IMAP human health Tier II assessment report for 2-propenoic acid, 2-methyl-, 2-hydroxyethyl ester – this report is publicly available on the NICNAS website: NICNAS IMAP-assessment ID 1187[5].

2-Hydroxyethyl methacrylate is also used in dental restorative products in Australia.

Scheduling status

2-Hydroxyethyl methacrylate is not currently scheduled. Following the March 2015 meeting of the Advisory Committee on Chemicals Scheduling, a new Schedule 5 entry was proposed for 2-hydroxyethyl methacrylate except when in nail preparations labelled "Avoid contact with skin". New Appendix E and Appendix F entries were also proposed for 2-hydroxyethyl methacrylate when in Schedule 5. The proposed implementation date was 1 February 2016.

The scheduling delegate subsequently became aware that 2-hydroxyethyl methacrylate is also used in dental restorative products for human use.

[5] IMAP - Human Health Tier II Assessment for 2-Propenoic acid, 2-methyl-, 2-hydroxyethyl ester <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1187>

Scheduling history

2-Hydroxyethyl methacrylate

Advisory Committee on Chemicals Scheduling: March 2015

The ACCS considered a proposal to create a new Schedule 5 entry for 2-hydroxyethyl methacrylate (primarily for use in cosmetics or domestic products). Concerns regarding skin sensitisation potential and evidence of eye irritation with 2-hydroxyethyl methacrylate were noted. The ACCS recommended inclusion of 2-hydroxyethyl methacrylate in Schedule 5, except when in nail preparations labelled "Avoid contact with skin". Appendix E and Appendix F statements were also proposed.

Other methacrylate esters

2-Hydroxyethyl methacrylate belongs to a group of chemicals known as methacrylate esters, and other chemicals in this group have been considered by National Drugs and Poisons Scheduling Committee (NDPSC) and Advisory Committee on Chemicals Scheduling (ACCS), for the same use and due to the same hazardous property of skin sensitisation. Two other chemicals belonging to this group of chemicals, namely ethyl methacrylate and methyl methacrylate are listed in the Poisons Standard.

National Drugs and Poisons Scheduling Committee: 2006-2008

The NDPSC considered ethyl methacrylate and methyl methacrylate several times over the period 2006-2008. The NDPSC decided to include ethyl methacrylate in Schedule 5 at concentrations above 1% as the low irritancy and skin sensitisation risks of ethyl methacrylate could be appropriately reduced through including a new Schedule 5 entry for cosmetic use, and to create an Appendix F entry providing appropriate warning statements and safety directions and that these risks are sufficiently reduced when there is ≤ 1% monomer present as a residue in a polymer as to warrant exclusion from the requirements of scheduling.

The NDPSC decided to include methyl methacrylate (MMA) in Schedule 6 for non-cosmetic uses at concentrations above 1% and Appendix C for all cosmetic uses. The NDPSC noted that the severe dermal irritancy, moderate respiratory irritancy and evidence of moderate sensitising potential of methyl methacrylate constituted a moderate potential for causing harm (when for non-cosmetic uses), the extent of which could be reduced through the use of appropriate packaging and labelling and that these risks are sufficiently reduced when there is ≤ 1% monomer present as a residue in a polymer as to warrant exclusion from the requirements of scheduling. However, the cosmetic use of MMA posed sufficient danger as to warrant prohibition of sale, supply and use through inclusion in Appendix C.

Advisory Committee on Chemicals Scheduling: July 2014

Another methacrylate ester, 2-hydroxypropyl methacrylate, was considered by the ACCS. The chemicals delegate's decision was to add the substance to schedule 5 in nail preparations except when labelled 'avoid contact with skin'. The chemicals delegate noted the toxicity of 2-hydroxypropyl methacrylate appears to be less severe than the methyl- and ethylmethacrylates currently listed in Schedule 5, 6 and Appendix C, although there is some potential for cross sensitisation to occur between these methacrylate derivatives when used in nail preparations. The implementation date for this decision is 1 January 2016. The final decision of 2-hydroxypropyl methacrylate is available at https://www.tga.gov.au/book/final-decisions-matters-referred-expert-advisory-committee-11-14#hydro

Pre-meeting public submissions

No submissions were received.

ACMS advice to the delegate

The ACMS recommended that 2-hydroxyethyl methacrylate be included in Schedule 5 except when included in dental restorative preparations for therapeutic use when labelled "Avoid contact with

skin" (this is in addition to the previously agreed exemption for nail preparations labelled "Avoid contact with skin").

The ACMS recommended an implementation date for the new Schedule 5 entry of 1 February 2016.

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

- Risks: irritation and skin sensitisation; and lower risk due to inhalation of the chemical.
- 2-Hydroxyethyl methacrylate is used in therapeutic goods for dental use that are regulated by the TGA.
- There were some concerns regarding the potential for occupational exposure of dental technicians.
- Labels of products containing 2-hydroxyethyl methacrylate should be required to include a warning statement regarding skin sensitisation.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[6];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that 2-hydroxyethyl methacrylate be included in Schedule 5 except when included in dental restorative preparations for therapeutic use when labelled "Avoid contact with skin" (this is in addition to the previously agreed exemption for nail preparations labelled "Avoid contact with skin").

The proposed implementation date is 1 February 2015.

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

- The main risks with 2-hydroxyethyl methacrylate are irritation and skin sensitisation. There were some concerns regarding the potential for occupational exposure of dental technicians.

[6] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

- 2-Hydroxyethyl methacrylate is used in therapeutic goods for dental use that are regulated by the TGA.
- The SUSMP Appendix A general exemption does not apply to dental restorative compounds, as they are not Class III medical devices.
- Exemption of 2-hydroxyethyl methacrylate from scheduling in products for therapeutic or dental use is appropriate. Dental restorative compounds are used by highly trained people and the 2-hydroxyethyl methacrylate is converted to the polymer form (cured by UV light). There is a low risk of deliberate or accidental misuse.
- There were some concerns regarding the potential for occupational exposure of dental technicians.
- The only effect of exempting dental restoratives from Schedule 5 (with products required to be labelled "Avoid contact with the skin") is that product labels would not require a "CAUTION" heading.
- Insufficient information is available to support any specific concentration cut-off for a scheduling exemption for 2-hydroxyethyl methacrylate in dental preparations. Therefore, dental products should be scheduled in the same way as nail preparations.
- Labels of products containing 2-hydroxyethyl methacrylate should be required to include a warning statement regarding skin sensitisation.

Schedule entry

SCHEDULE 5 – NEW ENTRY

2-HYDROXYETHYL METHACRYLATE except when included in dental restorative preparations for therapeutic use or in nail preparations when labelled "Avoid contact with skin".

APPENDIX E, PART 2 – NEW ENTRY

Poison	Standard statements
2-hydroxyethyl methacrylate	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

Poison	Warning statement	Safety direction
2-hydroxyethyl methacrylate	28. (Over) (Repeated) exposure may cause sensitisation.	4. Avoid contact with skin

1.6 Esomeprazole

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To amend the scheduling of esomeprazole to include oral preparations containing 20 mg or less of esomeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than seven days' supply from Schedule 3 to Schedule 2.

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

Substance summary

Esomeprazole is the S-isomer of the proton pump inhibitor (PPI), omeprazole, and is used similarly in the treatment of peptic ulcer disease and NSAID-associated ulceration, in gastro-oesophageal reflux disease, and in Zollinger-Ellison syndrome. Esomeprazole is given as the magnesium, sodium, or strontium salts but doses are calculated in terms of esomeprazole. Esomeprazole magnesium 22.2 mg, esomeprazole sodium 21.3 mg, and esomeprazole strontium 24.7 mg are each equivalent to about 20 mg of esomeprazole.

Scheduling status

Esomeprazole is currently listed in Schedules 3 and 4.

SCHEDULE 3

ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

SCHEDULE 4

ESOMEPRAZOLE except when included in Schedule 3.

Scheduling history

National Drugs and Poisons Schedule Committee: November 2000

The New Zealand Ministry of Health requested that the NDPSC consider scheduling esomeprazole to harmonise with New Zealand's inclusion of the substance in Schedule 1, Part 1 (equivalent to Schedule 4 in the SUSMP). The NDPSC supported harmonisation and included esomeprazole in Schedule 4.

Advisory Committee on Medicines Scheduling: November 2013

The ACMS considered an application to down-schedule from Schedule 4 to Schedule 3 esomeprazole in in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply. The ACMS advised the delegate to down-schedule esomeprazole to Schedule 3, as requested.

Pre-meeting public submissions

Seven submissions were received.

Three submissions supported the applicant's proposal to reschedule esomeprazole from Schedule 3 to Schedule 2 when in packs containing not more than seven days' supply.

Main points:

- Esomeprazole is available OTC in the USA.
- Recommend appropriate warning statements.

Three submissions opposed the rescheduling proposal. Main points:

- No monitoring of ongoing/long-term use of PPIs which may lead to adverse reactions.

- Need to ensure appropriate consultation and review by pharmacists.

One submission did not state a position. Main points:

- If esomeprazole down-scheduled then recommend all PPIs have new Schedule 2 entry.

ACMS advice to the delegate

The ACMS recommended that esomeprazole in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than seven days' supply, be down-scheduled from Schedule 3 to Schedule 2.

The committee also recommended to the delegate that consideration be given to down-scheduling the other OTC PPIs (i.e. lansoprazole, omeprazole and rabeprazole) from Schedule 3 to Schedule 2 in packs containing not more than seven days' supply.

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

- Esomeprazole is a safe and effective first line treatment for consumers with frequent symptoms of gastro-oesophageal reflux disease.
- Heartburn and other symptoms of gastro-oesophageal reflux disease are common.
- Esomeprazole has very low toxicity with short-term use.
- The proposed Schedule 2 pack size (seven days' supply), labelling (including Required Advisory Statements for Medicine Labels (RASML) warning statements) and provision of Consumer medicine information will help ensure appropriate use of esomeprazole as a Schedule 2 medicine.
- The current RASML label warnings for all OTC PPIs would apply to esomeprazole in Schedule 2 or Schedule 3.
- Esomeprazole may be more effective in the treatment of gastro oesophageal reflux disease than ranitidine which is currently available as an unscheduled medicine (seven days' supply) and as a Schedule 2 medicine (14 days' supply).

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[7];
- Other relevant information.

[7] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

Delegate's interim decision

The delegate's interim decision is that esomeprazole, in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than seven days' supply, be down-scheduled from Schedule 3 to Schedule 2.

The proposed implementation date is 1 February 2016.

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

- Esomeprazole is a safe and effective first line treatment for consumers with frequent symptoms of gastro-oesophageal reflux disease.
- Heartburn and other symptoms of gastro-oesophageal reflux disease are common.
- Esomeprazole has very low toxicity with short-term use.
- The proposed Schedule 2 pack size (seven days' supply), labelling (including RASML warning statements) and provision of Consumer medicine information will help ensure appropriate use of esomeprazole as a Schedule 2 medicine.
- The current RASML label warnings for all OTC PPIs would apply to esomeprazole in Schedule 2 or Schedule 3.
- Esomeprazole may be more effective in the treatment of gastro oesophageal reflux disease than ranitidine which is currently available as an unscheduled medicine (seven days' supply) and as a Schedule 2 medicine (14 days' supply).

Schedule entry

SCHEDULE 2 – NEW ENTRY

ESOMEPRAZOLE in oral preparations containing 20 mg or less of esomeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

SCHEDULE 3 – AMENDMENT

ESOMEPRAZOLE in oral preparations containing 20 mg or less of esomeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.

SCHEDULE 4 – AMENDMENT

ESOMEPRAZOLE except when included in Schedule 2 or 3.

1.7 Proton pump inhibitors

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- To create new Appendix H entries for the following Schedule 3 proton pump inhibitors (PPIs):
  - lansoprazole;

- omeprazole;
- pantoprazole; and
- rabeprazole.

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

Substance summary

Lansoprazole, omeprazole, pantoprazole and rabeprazole are PPIs. PPIs are used in the treatment of peptic ulcer disease and NSAID-associated ulceration, in gastro-oesophageal reflux disease, and in Zollinger-Ellison syndrome.

Scheduling status

Lansoprazole, omeprazole and rabeprazole are currently listed in Schedules 3 and 4.

Pantoprazole is currently listed in Schedules 2, 3 and 4.

LANSOPRAZOLE

SCHEDULE 3

LANSOPRAZOLE in oral preparations containing 15 mg or less of lansoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

SCHEDULE 4

LANSOPRAZOLE except when included in Schedule 3.

OMEPRAZOLE

SCHEDULE 3

OMEPRAZOLE in oral preparations containing 20 mg or less of omeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

SCHEDULE 4

OMEPRAZOLE except when included in Schedule 3.

RABEPRAZOLE

SCHEDULE 3

RABEPRAZOLE in oral preparations containing 10 mg or less of rabeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

SCHEDULE 4

RABEPRAZOLE except when included in Schedule 3.

PANTOPRAZOLE

SCHEDULE 2

PANTOPRAZOLE in oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

SCHEDULE 3

PANTOPRAZOLE in oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.

SCHEDULE 4

PANTOPRAZOLE except when included in Schedule 2 or 3.

Scheduling history

National Drugs and Poisons Schedule Committee: June 2005

The NDPSC included pantoprazole in Schedule 3, in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply (the NDPSC subsequently amended the implementation date until 1 May 2008). The NDPSC did not consider Appendix H listing at that time.

National Drugs and Poisons Schedule Committee: June 2009

The NDPSC agreed to down-schedule rabeprazole to Schedule 3 (with pack size and indication restrictions similar to those for pantoprazole). A request for Appendix H listing was rejected.

National Drugs and Poisons Schedule Committee: February 2010

The NDPSC decided that inclusion of pantoprazole in Appendix H listing was not appropriate.

Lansoprazole and omeprazole were scheduled similarly to pantoprazole and rabeprazole, to harmonise with New Zealand. In both cases, the NDPSC agreed that a consistent approach for all PPIs should be undertaken in relation to Appendix H listing, i.e. lansoprazole and omeprazole were not included in Appendix H.

National Drugs and Poisons Schedule Committee: June 2010

The NDPSC again rejected a proposal to include rabeprazole in Appendix H. The NDPSC generally agreed that an Appendix H listing was not appropriate at this time and that it would be beneficial for pharmacists to first become accustomed to having rabeprazole available as a Schedule 3 medicine.

Advisory Committee on Medicines Scheduling: November 2014

The ACMS recommended a new entry in Schedule 2 for pantoprazole when supplied in oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days of supply.

Advisory Committee on Medicines Scheduling: March 2015

The ACMS recommended inclusion of esomeprazole in Appendix H. The ACMS also proposed that the medicines delegate consider initiating a proposal to list all Schedule 3 proton pump inhibitors (PPIs) in Appendix H.

Pre-meeting public submissions

Three submissions were received.

All three submissions supported the scheduling proposal with one on the condition that all advertisements for these products highlight the mandatory role of the pharmacist in determining the suitability of the product for consumers.

ACMS advice to the delegate

The ACMS recommended that new Appendix H entries be created for the following Schedule 3 proton pump inhibitors: Lansoprazole, Omeprazole, Pantoprazole and Rabeprazole.

The ACMS recommended an implementation date of 1 February 2016.

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

The reasons for the recommendation comprised the following:

- The ACMS, at its March 2015 meeting, had recommended inclusion of esomeprazole in Appendix H.
- The delegate decided that esomeprazole would be included in Appendix H as of 1 October 2015.
- There are no relevant clinical differences between esomeprazole and the other over-the-counter (OTC) PPI medications that would affect their listing in Appendix H.
- All the OTC PPIs have similar mechanisms of action and similar efficacy and safety profiles.
- The same indications and Required Advisory Statements for Medicine Labels (RASML) label statement requirements apply to all OTC PPIs.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[8];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that new Appendix H entries be created for the following Schedule 3 proton pump inhibitors: Lansoprazole, Omeprazole, Pantoprazole and Rabeprazole.

The proposed implementation date is 1 February 2016.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: a) the risks and benefits of the use of the substance; b) the purposes for which a

[8] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

substance is to be used and the extent of use of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the decision comprised the following:

- The ACMS, at its March 2015 meeting, had recommended inclusion of esomeprazole in Appendix H.
- The delegate decided that esomeprazole would be included in Appendix H as of 1 October 2015.
- There are no relevant clinical differences between esomeprazole and the other over-the-counter (OTC) PPI medications that would affect their listing in Appendix H.
- All the OTC PPIs have similar mechanisms of action and similar efficacy and safety profiles.
- The same indications and Required Advisory Statements for Medicine Labels (RASML) label statement requirements apply to all OTC PPIs.

Schedule entry

APPENDIX H – NEW ENTRIES

Lansoprazole.

Omeprazole.

Pantoprazole.

Rabeprazole.

1.8 Levocetirizine

Scheduling proposal

The medicines scheduling delegate (the delegate) has referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

- Although levocetirizine is covered by the schedule entries for cetirizine, it is proposed to include specific entries for levocetirizine in Schedule 2, Schedule 4 and Appendix K in the Poisons Standard.

Consideration should include:

- whether all levocetirizine preparations for oral use should be in Schedule 2; or
- whether levocetirizine should be exempt from scheduling in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: (a) in a primary pack containing not more than five days' supply; and (b) labelled with a recommended daily dose not exceeding 5 mg of levocetirizine (i.e. consistent with the scheduling exemption for cetirizine).

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

Substance summary

Levocetirizine is the active enantiomer of cetirizine (5 mg of levocetirizine is equivalent to 10 mg of cetirizine).

Levocetirizine is an antihistamine, and is used for relief of symptoms of allergic conditions such as allergic rhinitis and chronic idiopathic urticaria. In Australia, levocetirizine is approved for use in adults and children aged 2 years and over. In some other countries, levocetirizine is approved for use in children from 6 months of age (e.g. in the US, levocetirizine is approved for relief of symptoms of

seasonal allergic rhinitis in adults and children aged from 2 years, and for relief of symptoms of perennial allergic rhinitis and chronic idiopathic urticaria in adults and children aged from 6 months).

Cetirizine is a piperazine derivative and metabolite of hydroxyzine. It is a long-acting, low-sedating antihistamine with some mast-cell stabilising activity.

Scheduling status

Levocetirizine is not currently listed in the Poisons Standard, but would be covered by the Schedule 2 and 4 entries for cetirizine.

The Standard for Uniform Scheduling of Medicines and Poisons (SUSMP) Part 1, Interpretation, point 1(2) states: "Unless the contrary intention appears a reference to a substance in a Schedule or an Appendix to this Standard includes: … (c) every salt, active principle or derivative of the substance, including esters and ethers, and every salt of such an active principle or derivative; … (e) every stereoisomer of the substance and every salt of such a stereoisomer; …".

Cetirizine is currently listed in Schedules 2 and 4.

SCHEDULE 2

CETIRIZINE 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 not more than 5 days' supply; and

(b) labelled with a recommended daily dose not exceeding 10 mg of cetirizine.

SCHEDULE 4

CETIRIZINE 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 not more than 5 days' supply; and

(ii) labelled with a recommended daily dose not exceeding 10 mg of cetirizine.

Cetirizine is also listed in Appendix K.

Scheduling history

Levocetirizine

No previous scheduling considerations. DPSSC, NDPSC and ACMS considerations of cetirizine make no mention of levocetirizine.

Cetirizine

Drugs and Poisons Schedule Standing Committee: May 1993

The DPSSC decided to include cetirizine in Schedule 4 and in Appendix K (Drugs required to be labelled with a sedation warning).

National Drugs and Poisons Scheduling Committee: May 1997

The NDPSC decided to include cetirizine in Schedule 3 as the only therapeutically active substance in divided preparations for oral use containing 10 mg or less of cetirizine. A limit on pack size was not considered necessary. Cetirizine remained in Schedule 4 except when included in Schedule 3.

National Drugs and Poisons Scheduling Committee: February 1998

The NDPSC decided to amend the Schedule 3 entry for cetirizine to include all oral formulations of cetirizine, when it was the only active substance in the preparation (the Schedule 3 entry was no longer to be restricted to divided preparations and the maximum dosage unit size was deleted).

National Drugs and Poisons Scheduling Committee: November 1999

The NDPSC decided to reschedule cetirizine in all preparations for oral use to Schedule 2. The Appendix H entry for cetirizine was deleted.

Advisory Committee on Medicines Scheduling: June 2012

The ACMS recommended that cetirizine should be exempt from scheduling, when in divided forms for oral use containing 10 mg or less of cetirizine hydrochloride per dose, in packs containing not more than 5 days' supply for the treatment of seasonal allergic rhinitis.

Pre-meeting public submissions

Two submissions were received.

One submission supported the proposal to include separate schedule entries for levocetirizine, but did not support a scheduling exemption of levocetirizine.

Main points:

- Risk of sedation and its potential impact on driving capacity.
- Levocetirizine is six times more likely to result in sedation than other non-sedating antihistamines.
- Combination with other impairing drugs (including alcohol) increases the opportunity for impairment.
- Inclusion of warnings on medicine packs is insufficient.

One submission supported the proposal to schedule levocetirizine as for cetirizine.

ACMS advice to the delegate

The ACMS recommended that a separate schedule entry in the Poisons Standard for levocetirizine be included in Schedule 2 and Appendix K, and that levocetirizine should be scheduled as for cetirizine.

The ACMS recommended an implementation date of 1 February 2016.

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

The reasons for the recommendation comprised the following:

- Levocetirizine is the active isomer of cetirizine. The risks and benefits of levocetirizine and cetirizine will be the same, so the scheduling outcomes for the two substances should also be the same, taking the 1:2 dose ratio into account. Scheduling exemption would be similar to other less-sedating antihistamines.
- The indications for levocetirizine are as for cetirizine.
- Levocetirizine has the same efficacy and safety profiles as cetirizine.
- Schedule entries for levocetirizine and cetirizine should therefore have the same outcome.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[9];
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that separate schedule entries be included in the Poisons Standard for levocetirizine in Schedule 2, Schedule 4 and Appendix K, and that levocetirizine should be scheduled as for cetirizine.

The proposed implementation date is 1 February 2016.

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

The reasons for the decision comprised the following:

- Levocetirizine is the active isomer of cetirizine. The risks and benefits of levocetirizine and cetirizine will be the same, so the scheduling outcomes for the two substances should also be the same, taking the 1:2 dose ratio into account. Scheduling exemption would be similar to other less-sedating antihistamines.
- The indications for levocetirizine are as for cetirizine.
- Levocetirizine has the same efficacy and safety profiles as cetirizine.
- Schedule entries for levocetirizine and cetirizine should therefore have the same outcome.

Schedule entry

SCHEDULE 2 – NEW ENTRY

LEVOCETIRIZINE 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 not more than 5 days' supply; and

(b) labelled with a recommended daily dose not exceeding 5 mg of levocetirizine.

SCHEDULE 4 – NEW ENTRY

LEVOCETIRIZINE except:

(a) when included in Schedule 2; or

[9] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015) <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

(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 not more than 5 days' supply; and

(ii) labelled with a recommended daily dose not exceeding 5 mg of levocetirizine.

APPENDIX K – NEW ENTRY

Levocetirizine