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

March 2015

(ACMS Meeting – 18 November 2014)

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

A delegate of the Secretary to the Department of Health hereby gives notice of the delegates' final decisions for amending the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* – SUSMP) under subsections 42ZCZS and 42ZCZX of the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (implementation date) of the decision.

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the November 2014 meeting of the Advisory Committee on Medicines Scheduling (ACMS #13);
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

A 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 14 August 2014 and 20 August 2014 - https://www.tga.gov.au/consultation-invitation/consultation-invitation-public-comment-acms-and-joint-accsacms-meetings-november-2014 and https://www.tga.gov.au/consultation-invitation/consultation-invitation-public-comment-out-session-acms-meeting-november-2014, respectively.

Interim decisions

The delegate's interim decisions on recommendations by the ACMS #13 were published on 5 February 2015 month year at https://www.tga.gov.au/scheduling-decision-interim/reasons-scheduling-delegates-interim-decision-and-invitation-further-comment-acms-february-2015. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions.

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

Final decisions

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

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the *Scheduling Policy Framework for Chemicals and Medicines* (SPF, 2010), available at https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals.

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the Poisons Standard are published electronically on ComLaw as amendments to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the Poisons Standard on ComLaw, is available at https://www.tga.gov.au/publication/poisons-standard-susmp.

Glossary

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

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

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)
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
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (formerly Office of Prescription and Non-prescription Medicines)
OOS	Out of session
OTC	Over-the-counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority existing chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted flow insert

Abbreviation	Name
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

Table of contents

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

1. Scheduling proposals referred to the November 2014 meeting of the Advisory Committee on Medicines Scheduling (ACMS# 13)

1.1 PERFORMANCE AND IMAGE ENHANCING DRUGS

Scheduling proposal

To include new entries for Growth Hormone Releasing Hormones and Analogues (GHRHs), Growth Hormone Secretagogues (GHSs), Growth Hormone Releasing Peptides (GHRPs) and Growth Hormone Variants, as well as new individual substance entries for CJC-1295, ipamorelin, GHPR-2, GHPR-6, hexarelin and AOD-9604 in Schedule 4 and Appendix D.

Substance summary

Growth Hormone Releasing Peptides (GHRP) are a class of compounds, which stimulate the release of growth hormone. GHRP variants include GHRP-2, GHRP-6, hexarelin, ipamorelin (Thomas et al, 2011) and agents with similar actions including CJC-1295 (Teichman et al, 2006, Acherman et al, 1999, Walker et al, 2006). These agents are considered peptide hormones. GHRPs are thought to act by stimulating the release of endogenous human growth hormone leading to pharmacological effects such as increased bone mineral density, increased lean muscle mass, modest improvements in strength and improved recovery from injuries such as fractures (Smith, 2005).

Scheduling status

The substances were not currently scheduled.

Scheduling history

These substances had not been previously considered for scheduling therefore scheduling history was not available.

Pre-meeting public submissions

Two submissions were received, both in relation to AOD-9604. One submission did not comment on the scheduling proposal, but wished to inform the committee that the substance is an ingredient in cosmetic products being sold overseas, has an International Nomenclature Cosmetic Ingredient (INCI) name of 27701 sh-Oligopeptide-74 and is published in the International Cosmetic Ingredient Dictionary and Handbook as well as the International Buyer's Guide.

The other submission commented on the consideration to place AOD-9604 in Appendix D. The submission supported listing in Schedule 4, but raised concerns that listing the substance in Appendix D would limit any future development work, including clinical trials that are currently being conducted on the substance. The submitter notes that there are currently 5 clinical trials notified to the TGA using this substance, with these approved clinical trials going ahead on the basis that the substance is safe for human use. Inclusion in Appendix D may place unnecessary burden on those conducting these clinical trials.

ACMS advice to the delegate

The ACMS recommended that Growth Hormone Releasing Hormones (GHRHs), Growth Hormone Secretagogues (GHSs), Growth Hormone Releasing Peptides (GHRPs) as well as new individual substance entries for CJC-1295, ipamorelin, pralmorelin (Growth Hormone Releasing Peptide-2), Growth Hormone Releasing Peptide-6, hexarelin and AOD-9604 be included in Schedule 4.

The ACMS recommended listing Growth Hormone Releasing Hormones (GHRHs), Growth Hormone Secretagogues (GHSs), Growth Hormone Releasing Peptides (GHRPs) as well as new individual substance entries for CJC-1295, ipamorelin, pralmorelin (Growth Hormone Releasing Peptide-2), Growth Hormone Releasing Peptide-6, hexarelin and AOD-9604 in Appendix D, Item 5.

The ACMS recommended an implementation date of 1 June 2015.

The reasons for the recommendation comprised the following:

- There is limited information on the risks and benefits of the substances as there has been minimal use under appropriate medical supervision. Risks from misuse are considered to be similar to those associated with the misuse of growth hormone.
- There is increasing evidence that the PIEDs are being advertised to attract a number of user markets including:
  - Strength enhancement/muscle enhancement
  - Anti-ageing
  - Fat loss
  - Injury rehabilitation
  - Libido enhancement
  - Growth hormone deficiency
- There is the potential for the side effects associated with use of growth hormone when growth hormone secretagogues are used, particularly if the use is not under medical supervision. There are limited data on the safety of intravenous and subcutaneous use of AOD-9604 and on the long-term oral use of AOD-9604 in doses in excess of those used in clinical trials.
- Many of the substances are injected. This carries additional risks compared with other routes of administration. Injections need to be administered by persons who use appropriate infection control procedures.
- There is misuse of the substances in sport and by body builders.
- There is evidence of involvement of organised crime in supply of the substances. The substances are offered for sale via the internet. Many of the substances are promoted as safe alternatives to traditional performance enhancing substances such as the anabolic steroids. Suppliers are making unproven assertions about the efficacy and safety of the substances.

Delegate's interim decision

The interim decision was to include in Schedule 4 and in Appendix D Item 5 Growth Hormone Releasing Hormones (GHRHs), Growth Hormone Secretagogues (GHSs), Growth Hormone Releasing Peptides (GHRPs) as well as new individual substance entries for CJC-1295, ipamorelin,

pralmorelin (Growth Hormone Releasing Peptide-2), Growth Hormone Releasing Peptide-6, hexarelin and AOD-9604.

The proposed implementation date was 1 June 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 a substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of a substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the recommendation comprised the following:

- The long-term safety of PIEDs is not established. The potential adverse effects may include those associated with administration of growth hormones.
- PIEDs have the potential for downstream health effects such as adverse cardiovascular and hormonal effects.
- AOD-9604 was initially developed as an anti-obesity drug, but the obesity program was discontinued in 2007 as the clinical trials did not show a meaningful weight loss outcome across the trial population. AOD-9604 is now being investigated in Phase II trials for cartilage repair.
- The limited safety data on AOD-9604 do not provide evidence that repeated intravenous or subcutaneous injections are safe or that long term use of oral doses in excess of those used in the clinical trials are safe.
- Scheduling of the substances would help ensure there is appropriate medical supervision of use and may make the substances more difficult to obtain without a lawful purpose.
- There is evidence of misuse of these substances.
- It would be appropriate that they are listed in Item 5 of Appendix D similar to anabolic and androgenic steroid hormones etc.
- There is limited information on the risks and benefits of the substances as there has been minimal use under appropriate medical supervision. Risks from misuse are considered to be similar to those associated with the misuse of growth hormone.
- There is increasing evidence that the PIEDs are being advertised to attract a number of user markets including:
  - Strength enhancement/muscle enhancement
  - Anti-ageing
  - Fat loss
  - Injury rehabilitation
  - Libido enhancement
  - Growth hormone deficiency
- There is the potential for the side effects associated with use of growth hormone when growth hormone secretagogues are used, particularly if the use is not under medical supervision. There

are limited data on the safety of intravenous and subcutaneous use of AOD-9604 and on the long-term oral use of AOD-9604 in doses in excess of those used in clinical trials.

- Many of the substances are injected. This carries additional risks compared with other routes of administration. Injections need to be administered by persons who use appropriate infection control procedures.
- There is misuse of the substances in sport and by body builders.
- There is evidence of involvement of organised crime in supply of the substances. The substances are offered for sale via the internet. Many of the substances are promoted as safe alternatives to traditional performance enhancing substances such as the anabolic steroids. Suppliers are making unproven assertions about the efficacy and safety of the substances.

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[1];
- Other relevant information.

Public submissions on the interim decision

One submission was received, which did not support the inclusion of AOD-9604 in Appendix D as it would create a burden for legitimate clinical development of the substance in those states and territories which adopt Appendix D and therefore be ineffective in those that do not adopt Appendix D.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Schedule entry

Schedule 4 – New entry

AOD-9604 (CAS No. 221231-10-3)

CJC-1295 (CAS No. 863288-34-0)

PRALMORELIN ((GROWTH HORMONE RELEASING PEPTIDE-2) (GHRP-2))

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

GROWTH HORMONE RELEASING PEPTIDE-6 (GHRP-6)

GROWTH HORMONE RELEASING HORMONES *(GHRHs)

GROWTH HORMONE RELEASING PEPTIDES *(GHRPs)

GROWTH HORMONE SECRETAGOGUES * (GHSs)

HEXARELIN

IPAMORELIN

Appendix D, Item 5 – New entry

AOD-9604 (CAS No. 221231-10-3)

CJC-1295 (CAS No. 863288-34-0)

PRALMORELIN ((GROWTH HORMONE RELEASING PEPTIDE-2) (GHRP-2))

GROWTH HORMONE RELEASING PEPTIDE-6 (GHRP-6)

GROWTH HORMONE RELEASING HORMONES (GHRHs) including those separately specified in Schedule 4.

GROWTH HORMONE RELEASING PEPTIDES (GHRPs) including those separately specified in Schedule 4.

GROWTH HORMONE SECRETAGOGUES (GHSs) including those separately specified in Schedule 4.

HEXARELIN

IPAMORELIN

1.2 PARACETAMOL/CAFFEINE

Scheduling proposal

To amend Schedule 2 entry to exempt paracetamol when compounded with caffeine, in a powder or granule product containing 1000mg or less of paracetamol and in tablets or capsules containing 500mg or less of paracetamol when paracetamol is the only therapeutic active constituent and when supplied in primary packs of not more than 20 tablets/caplets or 10 sachets of powders/granules.

Substance summary

The following information regarding the substance was provided by the applicant:

> "Paracetamol is used worldwide for its analgesic and antipyretic actions and has been available in Australia since 1956. Caffeine is a stimulant and acts as an analgesic adjuvant, whereby it augments the analgesic effects of pain relievers such as paracetamol. The combination of paracetamol/caffeine (2x500mg/65mg) is indicated for temporary relief of pain and discomfort associated with headaches, tension headaches, osteoarthritis, arthritis, cold and flu symptoms, toothache, dental procedures, muscular aches, sore through and period pain. It also reduces fever.
>
> Paracetamol/caffeine formulations have a long-established safety and efficacy profile over 25 years of use as an open-sale medicine in major markets around the world. The

paracetamol/caffeine combination analgesic was registered as a schedule 2 product in Australia and has been marketed since 2010. Since that time no new significant issues or potential risks have been reported.

Both paracetamol and caffeine are regarded as being well tolerated when used at therapeutic doses and there is a low risk of serious expected or serious unexpected adverse events with these products when taken either alone or in combination. Clinical data demonstrate that paracetamol combined with caffeine significantly out performs paracetamol alone. Paracetamol/caffeine formulations are well established globally. Such formulations are marketed in over 90 countries and have been available unscheduled ranging from 14 years to 25 years. Cumulative post-marketing experience to date with the sponsor's paracetamol/caffeine combination products is estimated to be in excess of 488 million patients and has revealed no adverse safety signals or reasons for concern with the use of this product in an open sale environment.

Evidence review and acceptance by the NDPSC in 2007, demonstrated that paracetamol/caffeine combination analgesics have a very low risk of nephrotoxicity. Similarly, the combination analgesics pose a very low risk of toxicity in overdosing with only two fatal cases reported in the USA. However, these cases involved other medications in addition to paracetamol/caffeine with the latter being available in very large pack sizes. Further, there are no known contraindications to the paracetamol/caffeine combination apart from hypersensitivity to the constituents."

Scheduling status

Paracetamol is currently listed in Schedule 2.

Schedule 2

PARACETAMOL for therapeutic use except:

(a) when included in Schedule 4;
(b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

    (i) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules;

    (ii) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

    (iii) not labelled for the treatment of children 6 years of age or less;

    (iv) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than, phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

    (i) packed in blister or strip packaging or in a container with a child-resistant closure;

    (ii) in a primary pack containing not more than 20 tablets or capsules;

(iii) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

(iv) not labelled for the treatment of children 6 years of age or less;

(v) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin.

Scheduling history

In Australia, the phenacetin ban was followed, in 1977, by a re-scheduling of all analgesic combinations containing two or more of paracetamol, aspirin, salicylamide or caffeine to Schedule 4 on the recommendation of the National Health and Medicine Research Council.

The scheduling of paracetamol and caffeine when combined in a compound analgesic as the only two active ingredients was amended from Schedule 4 to Schedule 2 by the NDPSC at its 50th Meeting in June 2007. Evidence reviewed by the Committee at that time conclusively demonstrated that the key ingredient in terms of analgesic overuse and nephropathy was phenacetin and not caffeine. It was agreed that the indications for use, safety profile and potential for misuse met the criteria for a Schedule 2 medicine.

At the time that decision was made, paracetamol/caffeine combinations were available over-the-counter in over 50 other countries and had been exempt from scheduling in a number of major markets that are similar to Australia in terms of population type and regulatory status. Experience with the unscheduled sale of this product was extensive: UK 19 years, Ireland 12 years and New Zealand for 7 years. However, the Committee determined not to consider paracetamol combined with caffeine for exemption from scheduling until market experience had been gained with use as a Schedule 2 product in Australia.

The scheduling of paracetamol and caffeine when combined in a compound analgesic as the only active ingredients was again reviewed by the NDPSC at its 57th Meeting in October 2009 after the Committee had received a request to reconsider the scheduling on the grounds of potential toxicity if used in excess. This issue had been extensively reviewed at the June 2007 meeting and it was decided that Schedule 2 remained appropriate.

Pre-meeting public submissions

Six public submissions were received.

Five of the submissions did not support the proposal while the sixth submission did. The former contend that potential risks of inadvertent use of caffeine in those at risk of an adverse event will be increased if selection of an analgesic is made without the assistance or intervention of a healthcare professional. There was also concern that the proposed exemption may result in an increase in liver damage due to excessive consumption of such a product. This was likely to result from people abusing these products as a source of stimulants.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of paracetamol when compounded with caffeine remains appropriate.

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

dosage, formulation, labelling, packaging and presentation of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the recommendation comprised the following:

- Potential risk of harm through excessive unintentional use of caffeine.
- No strong argument for increasing availability.
- Concern of the product being used with other caffeine containing products and concern about the toxicity of the combination in intentional overdose.
- Preference for combination analgesics to only be available where professional advice is available.
- There was not a supported argument for public health benefit. Risk of consumer confusion without access to advice.

Delegate's interim decision

The delegate's interim decision was that the current scheduling of paracetamol when compounded with caffeine 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 a substance; b) the purposes for which a substance is to be used and the extent of use of a substance; and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

- Potential risk of harm through excessive unintentional use of caffeine.
- No strong argument for increasing availability.
- Concern of the product being used with other caffeine containing products and concern about the toxicity of the combination in intentional overdose.
- Preference for combination analgesics to only be available where professional advice is available.
- There was not a supported argument for public health benefit.
- Risk of consumer confusion without access to advice.
- Risk of consumer confusion regarding their caffeine intake from multiple sources, given that many caffeine-containing products (including foods, drinks and dietary supplements, as well as medicinal products) are freely available to 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[2];
- Other relevant information.

Public submissions on the interim decision

One submission was received, which did not support the delegate's interim decision, as available data support that the fixed dose paracetamol/caffeine combination product provides clinically meaningful efficacy over paracetamol alone; has an excellent safety profile; a very low risk of nephrotoxicity, toxicity in overdose, misuse, abuse or illicit use; and a highly favourable risk/benefit profile.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.3 PARACETAMOL/IBUPROFEN

Scheduling proposal

To amend Appendix H to include a new entry for paracetamol/ibuprofen.

Substance summary

Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, post-operative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft tissue disorders such as sprains and strains. It is also used to reduce fever.

Paracetamol

Paracetamol is a p-aminophenol derivative that inhibits analgesic and antipyretic effects and weak anti-inflammatory activity. Paracetamol is used for the relief of mild to moderate pain.

Scheduling status

Paracetamol combined with ibuprofen is listed in Schedule 4 and Schedule 3.

Schedule 4

PARACETAMOL:

(a) when combined with aspirin or salicylamide or any derivative of these substances except when separately specified in these Schedules;

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

(b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;
(c) in slow release tablets or capsules containing more than 665 mg of paracetamol;
(d) in non-slow release tablets or capsules containing more than 500 mg of paracetamol;
(e) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol; or
(f) for injection.

Schedule 3

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less.

Scheduling history

In June 2010, the National Drugs and Poisons Schedule Committee (NDPSC) considered the scheduling of paracetamol in combination with ibuprofen. Paracetamol preparations containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine, effervescent agents or guaiphenesin) in packs of 25 or less were exempt from scheduling. However, when these preparations were combined with another therapeutically active ingredient they became Schedule 2. The NDPSC considered that the Schedule 2 entry remained appropriate, but noted the possibility that more robust evidence of additional risk could come to light through any application for product approval with the Therapeutic Goods Administration. The delegate confirmed the NDPSC's decision and the reasons for the decision in August 2010.

The medicines delegate referred the proposal to upschedule paracetamol/ibuprofen from Schedule 2 to Schedule 3 to the Advisory Committee on Medicines Scheduling (ACMS) in early 2011. The proposal was submitted by the Advisory Committee on Non-Prescription Medicines (ACNM) as they were currently assessing a product in which the sponsor did not satisfactorily establish the efficacy and safety of the product and that public health concerns raised during the assessment of the product could be addressed by access to a pharmacist. AFT Pharmaceuticals had submitted a product application with the TGA at the time of this item being considered by the delegate and ACMS.

The ACMS recommended that paracetamol/ibuprofen be rescheduled from Schedule 2 to Schedule 3 and the delegate agreed with this recommendation for the following reasons:

- There were concerns regarding the number of contraindications and precautions and whether consumers would be able to interpret these appropriately without a requirement for pharmacist advice. There were concerns regarding gastro-intestinal, renal and other adverse effects related to the potential interactions of ibuprofen and paracetamol. Also raised were concerns regarding the potential for paracetamol overdose.

- A lack of toxicity and clinical safety data for the combination. There was insufficient meaningful post-marketing data to ensure safe use without the need to consult with a pharmacist or GP.

In October 2012 the ACMS provided the medicines delegate with their recommendation to refuse the proposals to down-schedule paracetamol/ibuprofen for pack sizes of 12 units or less and to include paracetamol when combined with ibuprofen in Appendix H. The delegate agreed for the following reasons:

- Safety concerns with this combination since 2009 and that there had not been enough data provided to disprove these concerns.

- Lack of evidence to support rescheduling to Schedule 2. The Scheduling Policy Framework scheduling factors for Schedule 2 had not been satisfied, especially in relation to the risk profile of the product.
- Additive gastro-intestinal side effects.
- Concern about lack of professional intervention for this combination product to ensure safe and effective use.
- Concern with the lack of long-term evidence.
- Therapeutically sub-optimal combination.
- Potential for inadvertent misuse.
- No public benefit.
- No experience with the use of the product in Australia.

Inclusion of paracetamol in combination with ibuprofen in Appendix H did not have any public health benefit resulting from any promotional activities that could be quantified and that advertising of the product could potentially lead to inappropriate medication use.

Pre-meeting public submissions

Four public submissions were received.

Two submissions supported the proposal as advertising was considered to bring important benefits in terms of better information for consumers on the availability of a combination product with rapid and effective pain relief and reduced doses of analgesic. Responsible advertising will alert consumers that combination products are available from pharmacies with advice from the pharmacist. One submission opposed the proposal as it was believed that there would be no benefit to the consumer by amending Appendix H to include a new entry for paracetamol/ibuprofen.

One submission requested the involvement of the pharmacy profession in the development of any advertisement or promotional material should the proposal be approved.

The final submission, though not opposed to the proposal, considered that some risks needed to be taken into consideration and mitigated where possible prior to listing on Appendix H being approved.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of paracetamol when combined with ibuprofen remains appropriate.

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

The reasons for the recommendation comprised the following:

- Public health risk from advertising is that it would be seen as first line therapy.
- The argument raised for Appendix H was to transfer demand from codeine combination analgesics to non-codeine combination analgesics - there was inadequate evidence to substantiate this claim.

Delegate's interim decision

The delegate's interim decision is that the current scheduling of paracetamol when combined with ibuprofen 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 a substance; and f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the recommendation comprised the following:

- There are concerns regarding safety of paracetamol-ibuprofen combinations, particularly with respect to gastrointestinal bleeding (in comparison with ibuprofen alone) and perhaps renal adverse effects. Some pre-submissions indicated that paracetamol-ibuprofen combinations should not be not first line therapy for pain relief.
- The argument raised for Appendix H was to transfer demand from codeine combination analgesics to non-codeine combination analgesics - there was inadequate evidence to substantiate this claim.
- Pharmacists can recommend a paracetamol-ibuprofen combination product to consumers who request a Schedule 3 codeine-combination analgesic for pain relief. It is considered that more effective promotion of paracetamol-ibuprofen combination analgesic products to pharmacists would be more beneficial than advertising to 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[3];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

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

1.4 PARACETAMOL/PHENYLEPHRINE

Scheduling proposal

To include the following in Schedule 3:

- 500 mg of paracetamol when combined with more than 2.5 mg phenylephrine per tablet or capsule or caplet.
- Individually wrapped powders or sachets of granules containing paracetamol 1000 mg and more than 5 mg phenylephrine per dose.

To include in the following in Schedule 2:

- 500 mg of paracetamol when combined with 2.5 mg phenylephrine or less per tablet or capsule or caplet in packs containing more than 20 tablets or capsules or caplets per pack.
- Individually wrapped powders or sachets of granules containing paracetamol 1000 mg and 5 mg phenylephrine or less per dose in packs containing more than 10 such powders or sachets.

To exempt from scheduling the following:

- 500 mg of paracetamol when combined with 2.5 mg phenylephrine or less per tablet or capsule or caplet in packs containing 20 or less tablets or capsules or caplets per pack.
- Individually wrapped powders or sachets of granules containing paracetamol 1000 mg and 5 mg phenylephrine or less per dose in packs containing 10 or less such powders or sachets.

Substance summary

Paracetamol

Paracetamol is distinct from non-steroidal anti-inflammatory drugs (NSAIDs). It is a para-acetylaminophenol with both analgesic and antipyretic properties. Originally synthesized in the 1880s and first released for use on prescription in 1955 in the USA and on 1956 in UK. It has been available in most countries, without prescription, for many years. Recent data suggests it acts via a central mechanism, whereby it is deacetylated to 4-aminophenyl and then conjugated with arachidonic acid to form N-arachidonoylphenylamine which is an exogenous cannabinoid (Hogestatt ED et al. 2005).

Paracetamol has long been considered very safe, without the risks of gastric injury associated with aspirin and NSAIDs. But there are distinct risks of liver injury, usually following overdose situations. In response many international regulatory authorities have taken steps to reduce the pack sizes of paracetamol, and to restrict release in some environments to pharmacies. In the USA, FDA has required prescription acetaminophen, when it is usually combined with an opioid, to reduce the dose per dose unit to 325 mg, but without reducing the maximal daily dose. No change of dosing in the USA has yet come for OTC acetaminophen. Use of paracetamol should be kept to a minimum in patients with underlying liver and renal disease. It can reduce the effects of lithium, ACE inhibitors, beta blockers and methotrexate. However, it remains one of the safest and most effective analgesic drugs, particularly in the elderly where the risks of gastric bleeding with NSAIDs are more common, and carries minimal side effects.

Phenylephrine

Phenylephrine is a direct alpha-1 adrenergic agonist, with weak alpha-2 adrenergic agonist activity. It also has very weak beta-adrenergic effects, but at therapeutic doses there are no significant

stimulating beta-1 adrenergic effects on the heart, or on the bronchial airways, or on peripheral blood vessels. This contrasts with pseudoephedrine, which has greater beta-adrenergic activity. The effect on the alpha-adrenergic receptors leads to local vasoconstriction and shrinking of mucous membranes. There is no anti-histamine effect. The drug is readily and completely absorbed following oral administration, undergoing extensive first pass metabolism in the intestinal wall and in the liver leading to some variability in individual pharmacokinetics. Nasal decongestion is apparent within 15 to 20 minutes and persists for up to 4 hours (AHFS 2007).

Phenylephrine is readily eliminated by sulphate conjugation in the intestinal wall, and oxidative deamination by monoamine oxidative glucuronidation in the liver. Monoamine oxidase (MAO) inhibitors can enhance the limited potential of phenylephrine for cardiac and pressor effects, by reducing metabolism. As a largely specific alpha adrenergic drug, with very weak beta agonism, there is little direct cardiac effect. However, in higher doses, there can be increases in both systolic and diastolic blood pressure and a reflex bradycardia. As an adrenergic agonist there is the potential to interact with other sympathomimetic drugs. In overdose phenylephrine can cause hypertension, headaches seizures tachycardia, and vomiting. There has been no evidence from carcinogenicity studies in rodents of any enhanced cancer risk over prolonged exposure.

Scheduling status

Paracetamol in combination with phenylephrine is listed in Schedule 2. There is also a separate entry for phenylephrine in Schedule 2 and in Schedule 4.

Schedule 2

PARACETAMOL for therapeutic use except:

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

(vi) enclosed in a primary pack that contains not more than 12 such powders or sachets of granules;

(vii) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

(viii) not labelled for the treatment of children 6 years of age or less; and

(ix) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

(i) packed in blister or strip packaging or in a container with a child-resistant closure;

(ii) in a primary pack containing not more than 25 tablets or capsules;

(iii) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

(iv) not labelled for the treatment of children 6 years of age or less; and

(v) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin.

PHENYLEPHRINE except:

(a) when included in Schedule 4;
(b) in oral preparations containing 50 mg or less of phenylephrine per recommended daily dose in packs containing 250 mg or less of phenylephrine; or
(c) in topical eye or nasal preparations containing 1 per cent or less of phenylephrine.

Schedule 4

PHENYLEPHRINE

(a) in preparations for injection; or
(b) in preparations for human ophthalmic use containing 5 per cent or more of phenylephrine.

Scheduling history

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

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

In June 2011 the Advisory Committee on Medicines Scheduling was referred a proposal by the delegate to consider up-scheduling of five (5) then unscheduled substances contained in cold and cough preparations into Schedule 2. One of these substances was phenylephrine and many public submissions received rejected this proposal on the grounds of the paracetamol/phenylephrine exemptions in the Schedule 2 entry. The committee made similar comments and the delegate agreed that the current exempt from scheduling status of phenylephrine was appropriate.

Pre-meeting public submissions

Five public submissions were received. Many of the submissions referred to the article published in the New England Journal of Medicine (NEJM) when giving their reasons for either supporting or rejecting the proposal. Some submissions also noted that a similar proposal is to be considered by an upcoming meeting of the Medicines Classification Committee (MCC) in New Zealand.

Three of the submissions did not support the proposal highlighting the impact the change in scheduling would have on product currently on the market, industry, pharmacists and consumers. Two submissions noted that there has not been a history of concern with this combination of substances. One submission, referring to the NEJM article, believed that a lack of information about the study means that it cannot be relied upon as there is not a meaningful assessment of the results.

One submission supported the proposal noting the NEJM article which highlights risks to the consumer.

The fifth submission supported the proposal in principal, however felt that consideration needed to be given to the impact the potential rescheduling would have on pharmacists, industry and consumers.

ACMS advice to the delegate

The ACMS recommended that the current scheduling of paracetamol in conjunction with phenylephrine remains appropriate.

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

The reasons for the recommendation comprised the following:

- Application would result in all current OTC paracetamol/ phenylephrine products being up-scheduled to S3. Applicant's justification for changing current combination products from exempt or S2 to S3 is on theoretical basis only, and no evidence provided of clinical risk. Pharmacokinetic study found that co-administration of paracetamol with phenylephrine increased plasma phenylephrine levels - applicant says this has potential for cardiac safety risk in susceptible patients.

- TGA evaluator concluded that the consistent absence of any clinically meaningful effects on blood pressure (BP) or heart rate (HR) in the applicant's bioavailability studies, and the absence of any ADR reports of BP, HR or other cardiovascular problems, indicate that "there is no valid reason for concern and no need to take any regulatory against the combination products currently in the ARTG and available in the Australian market", i.e. no demonstrated safety risk, and no evidence provided of efficacy of paracetamol 1000 mg / phenylephrine HCl 5 mg adult dose.

- Paracetamol/phenylephrine combination products are used for indications such as relief of cold & flu symptoms, or sinus pain & congestion. There are currently approx. 200 OTC combination products (unscheduled or S2) on the ARTG.

- All current OTC paracetamol/phenylephrine combination products provide an adult dose of 1000 mg paracetamol / 10 mg phenylephrine HCl - these products are currently unscheduled or S2.

Delegate's interim decision

The ACMS recommended that the current scheduling of paracetamol in conjunction with phenylephrine remains appropriate.

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

The reasons for the recommendation comprised the following:

- Application would result in all current OTC paracetamol/ phenylephrine products being up-scheduled to S3. Applicant's justification for changing current combination products from exempt or S2 to S3 is on theoretical basis only, and no evidence provided of clinical risk. Pharmacokinetic study found that co-administration of paracetamol with phenylephrine increased plasma phenylephrine levels - applicant says this has potential for cardiac safety risk in susceptible patients.

- TGA evaluator concluded that the consistent absence of any clinically meaningful effects on blood pressure (BP) or heart rate (HR) in the applicant's bioavailability studies, and the absence of any ADR reports of BP, HR or other cardiovascular problems, indicate that "there is no valid reason for concern and no need to take any regulatory against the combination products currently in the ARTG and available in the Australian market", i.e. no demonstrated safety risk, and no evidence provided of efficacy of paracetamol 1000 mg / phenylephrine HCl 5 mg adult dose.
- All current OTC paracetamol/phenylephrine combination products provide an adult dose of 1000 mg paracetamol / 10 mg phenylephrine HCl - these products are currently unscheduled or S2.

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.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.5 NAPROXEN SCHEDULE 2

Scheduling proposal

The medicines scheduling delegate considered a proposal to amend the Schedule 2 naproxen entry to exclude naproxen in a dosage form of 200 mg or less of naproxen per dosage unit in packs of 12 or less dosage units with a maximum recommended daily dose of not more than 600 mg of naproxen, and when not labelled for the treatment of children 12 years of age or less.

Substance summary

The chemical name of naproxen is (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid. Its molecular formula is C14H14O3 and molecular weight is 230.3 g/mole. It is an odourless, white to

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

off-white crystalline substance which is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH.

Naproxen, a propionic acid derivative related to the arylacetic acid class of medicines is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. It is unrelated to salicylates and the corticosteroid hormones. Its indications include treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis; symptomatic treatment of primary dysmenorrhoea, and relief of acute and/or chronic pain states in which there is an inflammatory component and as an analgesic in acute migraine attack.

Both the naproxen base and the salt are rapidly and completely absorbed from the gastrointestinal tract, both circulating as the naproxen anion and the difference between them is that peak plasma levels of naproxen occur earlier following oral administration of naproxen sodium than naproxen. When administered as a sodium salt, naproxen sodium promptly dissolves in the gastric juice upon entering the stomach and immediately precipitates into fine particles of naproxen. The subsequent pharmacokinetics of the two formulations are identical. Steady state concentrations are achieved after four to five doses.

Poisoning with NSAIDs is not uncommon but rarely severe. In mild to moderate poisoning, gastrointestinal effects (e.g. dyspepsia, ulceration, bleeding) are most commonly reported. Renal dysfunction, most often in elderly patients, may occur. Mild central nervous system (CNS) effects include altered cognition, drowsiness, headache, and mood changes, especially in the elderly population. Severe poisoning is rare but can include CNS depression, hallucinations, seizures, renal failure, gastrointestinal bleeding, and metabolic acidosis.

Scheduling status

Naproxen is currently scheduled in Schedule 4, Schedule 3 and in Schedule 2 and listed in Appendix F with warning statements 101 and 104.

Schedule 4

NAPROXEN except when included in Schedule 3 or Schedule 2.

Schedule 3

NAPROXEN in modified release dosage form of 600 mg or less per dosage unit in packs of 16 or less dosage units when labelled not for the treatment of children under 12 years of age.

Schedule 2

NAPROXEN in divided preparations containing 250 mg or less of naproxen per dosage unit in packs of 30 or less dosage units.

Appendix F, Part 3

Poison	Warning statements	Safety direction
NAPROXEN	101 Don't use [this product/name of the product]: • If you have a stomach ulcer • In the last 3 months of pregnancy [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.] • If you are allergic to (name of substance) or anti-inflammatory medicines.	
	104 Unless a doctor has told you to, don't use [this product/name of the product]: • For more than a few days at a time • With other medicines containing (name of substance) or other anti-inflammatory medicines • If you have asthma • If you are pregnant [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea].	

Scheduling history

Naproxen first appeared in the Poisons Standard in June 1982 under Schedule 4, however, corresponding minutes cannot be located.

In February 1983, the Poisons Scheduling Committee (PSC) considered an application to reschedule naproxen from Schedule 4 to Schedule 3 when supplied in packs of 12 tablets for the treatment of the symptoms of dysmenorrhea. The committee noted the same decision was made in 1979 for a similar substance and the committee agreed that the toxicity, pharmacology and efficacy of naproxen indicated that it could be listed in Schedule 3.

The Department of Health Services, Tasmania requested the PSC to reconsider the Schedule 3 entry for naproxen in February 1985, after reports of massive internal bleeding occurred after ingesting the substance. The committee asked the secretary to contact the company and request sales information on both S3 and S4 products. It was noted in the November 1985 meeting that the company provided statistics to show there was not much evidence of this side effect and decided that the Schedule 3 entry should not be altered.

In November 1987, the committee noted that the Australian Drug Evaluation Committee (ADEC) would not support a Schedule 2 entry for naproxen.

A request for a Schedule 2 entry for naproxen sodium when labelled for the treatment of spasmodic dysmenorrhoea in packs of 12 or less was noted by the Drugs and Poisons Scheduling Committee (DPSC) in August of 1988. It was rejected as the submission had pages missing.

The request was resubmitted and discussed at the August 1989 committee meeting. The committee supported the Schedule 2 proposal on the grounds that it did not present an apparent public health hazard.

In November 1989, the committee considered a rescheduling application from Schedule 4 to Schedule 3 for naproxen. During this review, the committee noted strong anecdotal evidence of gastrointestinal bleeding caused by NSAIDs that had not been reported and which was at least partly dose-related. It also noted that there was little evidence to state that naproxen was more effective than aspirin or paracetamol; therefore there was no therapeutic gap to be filled by the substance. The members were not satisfied that the case for Schedule 3 was convincing and considered the application lacked evidence. The committee did not support the proposal.

In February 1991, Western Australian Health informed the committee that they would only accept the Schedule 2 entry for naproxen when labelled with an appropriate warning statement. The committee preferred the statement 'Warning - This medication may be dangerous when used in large amounts or for a long time'.

In November 1998, the NDPSC considered a proposal to amend the Schedule 2 entry to include packs of 10 tablets, each containing 220mg of naproxen for short term pain management. Public submissions supported a Schedule 3 entry to address concerns over inappropriate use. ADEC stated that product information and labels should provide warning statements and indicate short term use only. The members stated that incidence of gastrointestinal issues associated with naproxen was not greater than with ibuprofen and aspirin. The committee decided that a Schedule 3 entry for the indicated use was more appropriate along with Appendix F warning statement 71. The Schedule 2 entry was amended to allow preparations containing 250 mg or less per dosage unit in packs of 20 or less dosage units.

In November 1999, the committee agreed to reschedule the Schedule 3 entry to Schedule 2 after considering the safety data was similar to that of other NSAIDs already listed in Schedule 2. The NZ member advised that their committee had made a similar decision on the same grounds. The Appendix F warning was to be linked to the Schedule 2 entry.

In February 2000, the committee received comments regarding the perceived inadequacy of labelling for naproxen. The committee decided to await the outcome of a review of product labelling being conducted by the TGA before making decisions regarding changes to labelling.

In August 2001, the committee considered a proposal to exempt naproxen when in 250 mg or less per dosage unit, in packs of 24 or less dosage units, for the short-term analgesic therapy of dysmenorrhoea. While the committee noted a number of key points justifying the proposal, a number of public submissions did not support it on the grounds of maintaining access to professional advice. The evaluation report did not support the proposal due to a lack of evidence regarding safety and the need to be able to access advice and counselling. A Committee member raised concerns on potential misuse of the product, as it may be used routinely for headache rather than dysmenorrhoea. Another concern was that if a product was granted an unscheduled status based on one indication (i.e. for dysmenorrhoea), while the same product remained in S2 for all other indications, and the trade name remained unchanged as proposed, then it would be likely that

consumers would use the product routinely for general pain relief. The committee decided that the Schedule 2 entry remained appropriate.

In June 2003, a review of non-prescription analgesics was carried out, mainly in regards to proposed warning statements for inclusion in Appendix F. Outcomes of the review were provided, but the committee felt that further consultation with industry was required. The committee agreed to transitional arrangements in October 2003, supporting the outcome of the review. Warning statements 101 and 104 were to come into effect 1 May 2005.

In October 2004, the committee reviewed the warning statements for NSAIDs. Concerns were raised regarding warning statement 101 not warning against use in patients with a history of stomach ulcers and 104 did not warn against use in elderly patients. The committee discussed the advice sought from the Medicines Evaluation Committee (MEC) and comments received from the Gastroenterological Society regarding whether all non-prescription diclofenac should carry the same warning statements as the other NSAIDs, e.g. ibuprofen, aspirin, naproxen and mefenamic acid for consistency. The committee decided it was preferable for the MEC to consider the comments from the Gastroenterological Society and for the MEC to make the necessary labelling changes.

In June 2007, the NDPSC considered a proposal to apply a maximum daily dose restriction to the Schedule 2 entry for Naproxen. This issue arose when it was noted that naproxen didn't have a maximum daily dose restriction when considering entries for similar substances which did have restrictions. It was felt that this inconsistency needed to be addressed. Public submissions supported the proposal, so that NSAIDs entries could be consistent and provided suggested cut off limits. The Committee discussed this and felt that the regulator would have assessed this data in allowing the current maximum daily doses to be set as part of their registered indications. It was felt that that there was no requirement for the Committee to pursue consistency for consistency's sake and therefore did not support the proposal.

It was noted in June 2008 that the scheduling entry for naproxen was essentially harmonised between Australia and New Zealand.

A modified release dosage form of naproxen was referred to the Advisory Committee on Medicines Scheduling in March 2014, with the medicines delegate seeking their expert opinion. Considering their advice, the evaluation report and public submissions received, the delegate decided that modified release naproxen should be listed in Schedule 3 as the advice of a pharmacist would be warranted in the first stage of a new product being introduced to the market and that the advice of the pharmacist would enhance the quality use of this medicine such that inappropriate use of naproxen ER for more transient pain does not occur, where there are many more appropriate shorter acting alternatives.

Pre-meeting public submissions

Five public submissions were received. One supported the proposal with appropriate wording that is consistent with other OTC medicines such as paracetamol and ibuprofen. The others opposed any amendment to the S2 entry for naproxen due to potential risks if the substance is accessible to consumers outside registered pharmacy premises.

ACMS advice to the delegate

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

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

substance is to be used and the extent of use of a substance; c) the toxicity of a substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; and e) the potential for abuse of a substance.

The reasons for the recommendation comprised the following:

- Risks: GI disorders, allergic reactions, renal toxicities & cardio vascular adverse events are some of the common risks. Potential for inappropriate use & overuse of the product, especially if advice from a pharmacist is not available if the product was to be exempt from scheduling.
- GI risk with naproxen is greater than with ibuprofen.
- It has analgesic, anti-inflammatory & anti-pyretic properties. It is used for the relief of a number of common conditions where pain and or inflammation are a component.
- Poisoning with NSAIDs is known especially in high doses. Common adverse effects include dyspepsia, ulceration, GI bleeding, headaches, confusion & drowsiness. There are no new adverse events associated with this proposed product.
- The TGA would be responsible for the registered product label. It is to be labelled not for the treatment of children 12 years of age or less. Labelling will be in accordance with mandatory Medicines Advisory Statements Specifications 7, including the Required Advisory Statements for Medicine Labelling (RASML) (101 & 104).
- Low potential for abuse.

Delegate's interim decision

The interim decision is that the current scheduling of naproxen remains appropriate.

Reasons for the decision are:

- Risks: GI disorders, allergic reactions, renal toxicities & cardio vascular adverse events are some of the common risks. Potential for inappropriate & overuse of the product, especially if advice from a pharmacist is not available if the product was to be exempt from scheduling. GI risk with naproxen is greater than with ibuprofen;
- It has analgesic, anti-inflammatory & anti-pyretic properties. It is used for the relief of a number of common conditions where pain and or inflammation are a component;
- Poisoning with NSAIDs is known especially in high doses. Common adverse effects include dyspepsia, ulceration, GI bleeding, headaches, confusion & drowsiness. There are no new adverse events associated with this proposed product;
- The TGA would be responsible for the registered product label. It is to be labelled not for the treatment of children 12 years of age or less. Labelling will be in accordance with mandatory Medicines Advisory Statements Specifications 7, including the Required Advisory Statements for Medicine Labelling (RASML) (101 & 104);
- Low potential for abuse; and
- In view of increased risk versus other NSAIDS which are excluded.

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[5];
- Other relevant information.

Public submissions on the interim decision

One submission was received which did not support the delegate's interim decision as the risks associated with the use of naproxen are no greater than other analgesics such as aspirin, ibuprofen or paracetamol.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.6 NAPROXEN APPENDIX H

Scheduling proposal

The medicines scheduling delegate considered a proposal to include naproxen in Appendix H.

Substance summary

The chemical name of naproxen is (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid. Its molecular formula is C14H14O3 and molecular weight is 230.3 g/mole. It is an odourless, white to off-white crystalline substance which is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH.

Naproxen, a propionic acid derivative related to the arylacetic acid class of medicines is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. It is unrelated to salicylates and the corticosteroid hormones. Its indications include treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis; symptomatic treatment of primary dysmenorrhoea, and relief of acute and/or chronic pain states in which there is an inflammatory component and as an analgesic in acute migraine attack.

Both the naproxen base and the salt are rapidly and completely absorbed from the gastrointestinal tract, both circulating as the naproxen anion and the difference between them is that peak plasma levels of naproxen occur earlier following oral administration of naproxen sodium than naproxen. When administered as a sodium salt, naproxen sodium promptly dissolves in the gastric juice upon entering the stomach and immediately precipitates into fine particles of naproxen. The subsequent pharmacokinetics of the two formulations are identical. Steady state concentrations are achieved after four to five doses.

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

Scheduling status

Naproxen is currently scheduled in Schedule 4, Schedule 3 and in Schedule 2 and listed in Appendix F with warning statements 101 and 104.

Schedule 4

NAPROXEN except when included in Schedule 3 or Schedule 2.

Schedule 3

NAPROXEN in modified release dosage form of 600 mg or less per dosage unit in packs of 16 or less dosage units when labelled not for the treatment of children under 12 years of age.

Schedule 2

NAPROXEN in divided preparations containing 250 mg or less of naproxen per dosage unit in packs of 30 or less dosage units.

Appendix F, Part 3

Poisons	Warning statements	Safety direction
NAPROXEN	101 Don't use [this product/name of the product]: • If you have a stomach ulcer • In the last 3 months of pregnancy [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.] • If you are allergic to (name of substance) or anti-inflammatory medicines.	
	104 Unless a doctor has told you to, don't use [this product/name of the product]: • For more than a few days at a time • With other medicines containing (name of substance) or other anti-inflammatory medicines • If you have asthma • If you are pregnant [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea].	

Scheduling history

Naproxen first appeared in the Poisons Standard in June 1982 under Schedule 4; however, corresponding minutes cannot be located.

In February 1983, the Poisons Scheduling Committee (PSC) considered an application to reschedule naproxen from Schedule 4 to Schedule 3 when supplied in packs of 12 tablets for the treatment of the symptoms of dysmenorrhea. The committee noted the same decision was made in 1979 for a similar substance and the committee agreed that the toxicity, pharmacology and efficacy of naproxen indicated that it could be listed in Schedule 3.

The Department of Health Services, Tasmania requested the PSC to reconsider the Schedule 3 entry for naproxen in February 1985, after reports of massive internal bleeding occurred after ingesting the substance. The committee asked the secretary to contact the company and request sales information on both S3 and S4 products. It was noted in the November 1985 meeting that the company provided statistics to show there was not much evidence of this side effect and decided that the Schedule 3 entry should not be altered.

In November 1987, the committee noted that the Australian Drug Evaluation Committee (ADEC) would not support a Schedule 2 entry for naproxen.

A request for a Schedule 2 entry for naproxen sodium when labelled for the treatment of spasmodic dysmenorrhoea in packs of 12 or less was noted by the Drugs and Poisons Scheduling Committee (DPSC) in August of 1988. It was rejected as the submission had pages missing.

The request was resubmitted and discussed at the August 1989 committee meeting. The committee supported the Schedule 2 proposal on the grounds that it did not present an apparent public health hazard.

In November 1989, the committee considered a rescheduling application from Schedule 4 to Schedule 3 for naproxen. During this review, the committee noted strong anecdotal evidence of gastrointestinal bleeding caused by NSAIDs that had not been reported and which was at least partly dose-related. It also noted that there was little evidence to state that naproxen was more effective than aspirin or paracetamol; therefore there was no therapeutic gap to be filled by the substance. The members were not satisfied that the case for Schedule 3 was convincing and the application lacked evidence. The committee did not support the proposal.

In February 1991, Western Australian Health informed the committee that they would only accept the Schedule 2 entry for naproxen when labelled with an appropriate warning statement. The committee preferred the statement ‘Warning - This medication may be dangerous when used in large amounts or for a long time’.

In November 1998, the NDPSC considered a proposal to amend the Schedule 2 entry to include packs of 10 tablets, each containing 220mg of naproxen for short term pain management. Public submissions supported a Schedule 3 entry to address concerns over inappropriate use. ADEC stated that product information and labels should provide warning statements and indicate short term use only. The members stated that incidence of gastrointestinal issues associated with naproxen was not greater than with ibuprofen and aspirin. The committee decided that a Schedule 3 entry for the indicated use was more appropriate along with Appendix F warning statement 71. The Schedule 2 entry was amended to allow preparations containing 250 mg or less per dosage unit in packs of 20 or less dosage units.

In November 1999, the committee agreed to reschedule the Schedule 3 entry to Schedule 2 after considering the safety data was similar to that of other NSAIDs already listed in Schedule 2. The

NZ member advised that their committee had made a similar decision on the same grounds. The Appendix F warning was to be linked to the Schedule 2 entry.

In February 2000, the committee received comments regarding the perceived inadequacy of labelling for naproxen. The committee decided to await the outcome of a review of product labelling being conducted by the TGA before making decisions regarding changes to labelling.

In August 2001, the committee considered a proposal to exempt naproxen when in 250 mg or less per dosage unit, in packs of 24 or less dosage units, for the short-term analgesic therapy of dysmenorrhoea. While the committee noted a number of key points justifying the proposal, a number of public submissions did not support it on the grounds of maintaining access to professional advice. The evaluation report did not support the proposal due to a lack of evidence regarding safety and the need to be able to access advice and counselling. A Committee member raised concerns on potential misuse of the product, as it may be used routinely for headache rather than dysmenorrhoea. Another concern was that if a product was granted an unscheduled status based on one indication (i.e. for dysmenorrhoea), while the same product remained in S2 for all other indications, and the trade name remained unchanged as proposed, then it would be likely that consumers would use the product routinely for general pain relief. The committee decided that the Schedule 2 entry remained appropriate.

In June 2003, a review of non-prescription analgesics was carried out, mainly in regards to proposed warning statements for inclusion in Appendix F. Outcomes of the review were provided, but the committee felt that further consultation with industry was required. The committee agreed to transitional arrangements in October 2003, supporting the outcome of the review. Warning statements 101 and 104 were to come into effect 1 May 2005.

In October 2004, the committee reviewed the warning statements for NSAIDs. Concerns were raised regarding warning statement 101 not warning against use in patients with a history of stomach ulcers and 104 did not warn against use in elderly patients. The committee discussed the advice sought from the Medicines Evaluation Committee (MEC) and comments received from the Gastroenterological Society regarding whether all non-prescription diclofenac should carry the same warning statements as the other NSAIDs, e.g. ibuprofen, aspirin, naproxen and mefenamic acid for consistency. The committee decided it was preferable for the MEC to consider the comments from the Gastroenterological Society and for the MEC to make the necessary labelling changes.

In June 2007, the NDPSC considered a proposal to apply a maximum daily dose restriction to the Schedule 2 entry for Naproxen. This issue arose when it was noted that naproxen didn't have a maximum daily dose restriction when considering entries for similar substances which did have restrictions. It was felt that this inconsistency needed to be addressed. Public submissions supported the proposal, so that NSAIDs entries could be consistent and provided suggested cut off limits. The Committee discussed this and felt that the regulator would have assessed this data in allowing the current maximum daily doses to be set as part of their registered indications. It was felt that that there was no requirement for the Committee to pursue consistency for consistency's sake and therefore did not support the proposal.

It was noted in June 2008 that the scheduling entry for naproxen was essentially harmonised between Australia and New Zealand.

A modified release dosage form of naproxen was referred to the Advisory Committee on Medicines Scheduling in March 2014, with the medicines delegate seeking their expert opinion. Considering their advice, the evaluation report and public submissions received, the delegate decided that modified release naproxen should be listed in Schedule 3 as the advice of a pharmacist would be

warranted in the first stage of a new product being introduced to the market and that the advice of the pharmacists would enhance the quality use of this medicine such that inappropriate use of naproxen ER for more transient pain does not occur, where there are many more appropriate shorter acting alternatives.

Pre-meeting public submissions

Four public submissions were received. Three submissions supported the proposal as it was considered it would better inform the public of products available without prescription. One requested that the pharmacy profession have input into the development of any advertisement or promotional material.

One public submission opposed the proposal as no benefit to the consumer would result from advertising.

ACMS advice to the delegate

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

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

The reasons for the recommendation comprised the following:

- The Schedule 3 entry for a sustained released product was recently resolved. There is an inadequate body of evidence to support Appendix H listing.

Delegate's interim decision

The interim decision is that the current scheduling of naproxen remains appropriate.

Reasons for the decision are:

- Schedule 2 naproxen products can currently be advertised to consumers, and there does not appear to be any additional public health benefit in advertising modified release formulations of naproxen.
- Concern that advertising of the Schedule 3 product might encourage consumers to ask for the modified release product when use of conventional lower dose product might be more appropriate.
- Modified release naproxen has only recently been included in Schedule 3. No Schedule 3 naproxen products are currently registered in the Australian Register of Therapeutic Goods (ARTG), and consequently there is no experience with marketing Schedule 3 modified release naproxen products in Australia.
- The Schedule 3 entry for a modified released product was recently resolved.
- S3 entry is for a modified release formulation.
- No additional benefit in advertising the S3 product as already advertising allowed for S2 product. There is an inadequate body of evidence to support Appendix H listing.

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.

Public submissions on the interim decision

One submission was received which did not support the delegate's interim decision as naproxen is substantially safe for short term treatment and the potential for harm from inappropriate use is low. Advertising the availability of safe, proven and affordable medicine would increase consumer awareness of a medicine that may provide a useful long-lasting analgesic.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.7 BENZYDAMINE

Scheduling proposal

To exempt from scheduling benzydamine in preparations for topical use containing 3 mg or less of benzydamine in divided oral preparations and 3 mg/mL or less in undivided oral preparations in a pack of 50 mL or less.

Substance summary

Benzydamine lozenges and throat sprays are currently marketed for management of sore throats and other painful conditions of the mouth. If the proposal is accepted, such product would become available outside pharmacies. The question in this evaluation is whether or not the quality use of benzydamine can be achieved through labelling and packaging alone without access to advice of a pharmacist and whether wider availability of benzydamine is likely to lead to abuse or misuse.

In the management of common sore throats, the application reasonably argues that a patient can self-manage the ailment without intervention from a health professional (provided instructions are followed) as common sore throats are transient and the community has considerable experience with the condition. It also has a low abuse potential.

However, the application fails to address whether or not quality use of benzydamine can be achieved for other marketed indications, i.e. mouth ulcers, redness and inflammatory conditions of the mouth, pain following mouth and throat conditions, radiation mucositis, and pain following dental procedures. For some of these conditions, the aetiologies of the ailments are less clear and consumers would benefit from advice from a pharmacist, particularly for first time users.

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

Scheduling status

Benzydamine is currently listed in Schedules 2 and 4.

Schedule 4

BENZYDAIME except:

(a) when included in Schedule 2; or
(b) in preparations for dermal use.

Schedule 2

BENZYDAIME in preparations for topical use, except in preparations for dermal use.

Scheduling history

Benzydamine was first considered in November 1969 and recommended it be included in Schedule 4.

The Drugs and Poisons Scheduling Committee, in 1986, considered a proposal to down schedule benzydamine to Schedule 2 after two products - a 3% topical cream for inflamed muscles and a 0.15% oral rinse for the oral cavity - were approved for marketing. Based on the toxicity and side effect data, product labelling restricting use to 14 days for the cream and 7 days for the oral rinse and its documented safety for topical use, the committee recommended a new Schedule 2 entry for topical use containing 3 per cent or less of benzydamine.

In February 1999, the Trans-Tasman Harmonisation Working Party (TTHWP) advised that the National Drugs and Poisons Scheduling Committee (NDPSC) should amend the Schedule 2 entry to read "Benzydamine in preparations for topical use." The NDPSC noted that this amendment was to be considered later in the meeting as a part of a company submission.

That company submission was from 3M Pharmaceuticals for Difflam 5% topical gel, requesting that benzydamine in 5% preparations be moved from Schedule 4 to Schedule 2. Noting no difference in the adverse effects between the 3% and 5% product, the similar toxicity profile to other non-steroidal anti-inflammatory drug (NSAIDs) topical treatments already in Schedule 2 and the TTHWP recommendation, the NCPSC decided to amend the Schedule 2 entry to Benzydamine in preparations for topical use.

The NDPSC considered the scheduling of benzydamine for dermal use in February 2007. The committee agreed to exempt benzydamine for dermal use from scheduling given its indications for use and safety profile. It had been noted by the committee that other NSAIDs for dermal use were already exempt from scheduling and the level of adverse drug reactions with benzamine was similar to these exempt substances.

Pre-meeting public submissions

Three public submissions were received. Two submissions did not support the proposal and believe the substance should remain in a pharmacy setting so that consumers have access to health professionals who can determine the nature and cause of the condition being treated, and determine a more suitable treatment or referral to a doctor, if required. One submission stated that they may provide further comment on publication of the interim decision.

ACMS advice to the delegate

The ACMS recommended that benzydamine be exempt from Schedule 2 in preparations for topical use containing 3 mg or less of benzydamine in divided oral preparations and 3 mg/mL (0.3%) or less in undivided oral preparations in a pack containing 50 mL or less.

The ACMS recommended an implementation date of 1 June 2015.

The ACMS also recommended that the TGA should consider whether the Required Advisory Statements for Medicine Labels (RASML) should include any requirements for benzydamine.

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

The reasons for the recommendation comprised the following:

- Minimal risk of masking a condition with short-term use. Risk of substance is such that unscheduled status is acceptable and there is a potential benefit in wider access.
- Surgery and radiation therapy are managed interventions and under clinical supervision.
- Established safety profile of benzydamine in preparations for topical oral use.
- Limited potential for abuse/misuse.

Delegate's interim decision

The delegate's interim decision is that benzydamine be exempt from Schedule 2 in preparations for topical use containing 3 mg or less of benzydamine in divided oral preparations and 3 mg/mL (0.3%) or less in undivided oral preparations in a pack containing 50 mL or less with an implementation date of 1 June 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 a substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of a substance; and e) the potential for abuse of a substance.

The reasons for the recommendation comprised the following:

- As stated by the external evaluator it is accepted that conditions such as sore throats, mouth ulcers and redness and inflammatory conditions of the mouth are amenable to safe self-treatment by consumers without access to a health professional.
- Support for the requested scheduling exemption was provided by the availability for many years of unscheduled local anaesthetic preparations for relief of sore throats (e.g. benzocaine, lignocaine) without safety issues arising. Benzydamine lozenges and mouth sprays would provide a different therapeutic option for relief of uncomplicated sore throats.
- Patients with conditions such as radiation mucositis and those who have undergone mouth or throat surgery or dental procedures would be under the care of a medical or dental professional. Surgeons and dentists may initially prescribe benzydamine mouthwash for relief of pain associated with these conditions (and a 500 mL mouthwash is on the PBS for radiation-induced mucositis and as a PBS Dental item), but consumers could subsequently use benzydamine lozenges or mouth spray for these indications.

- Established safety profile of benzydamine in preparations for topical oral use.
- Limited potential for abuse/misuse.
- Similar risks apply to both divided and undivided oral benzydamine preparations for topical use, provided an appropriate pack size limit is set for undivided preparations. There have been some reports of abuse of benzydamine but it was considered that a 50 mL pack size limit for undivided oral preparations adequately addressed concerns about abuse of unscheduled benzydamine products.
- A maximum pack size was not considered necessary for divided oral preparations. Current scheduling exemptions for lozenges containing local anaesthetic substances did not include a pack size limit.
- Minimal risk of masking a condition with short-term use. Risk of substance is such that unscheduled status is acceptable and there is a potential benefit in wider access.

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.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate has made a minor amendment to the schedule entry published in the interim decision. The delegate reasons for the final decision are:

- Minimal risk of masking a condition with short-term use. Risk of substance is such that unscheduled status is acceptable and there is a potential benefit in wider access.
- Surgery, radiation therapy are managed interventions and under clinical supervision.
- Established safety profile.
- Limited potential for abuse/misuse.

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

Schedule entry

Schedule 2 - Amended entry:

BENZYDAMINE in preparations for topical use, except:

(a) in preparations for dermal use;
(b) in divided topical oral preparations containing 3 mg or less of benzydamine; or
(c) in undivided topical oral preparations containing 0.3 per cent or less of benzydamine in a primary pack containing not more than 50 mL.

Schedule 4 - Amended entry:

BENZYDAMINE except:

(a) when included in Schedule 2;
(b) in preparations for dermal use;
(c) in divided topical oral preparations containing 3 mg or less of benzydamine; or
(d) in undivided topical oral preparations containing 0.3 per cent or less of benzydamine in a primary pack containing not more than 50 mL.

1.8 PANTOPRAZOLE

Scheduling proposal

To amend Schedule 2 to create a new entry for pantoprazole when supplied in oral preparations containing 20mg 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.

To create two new warning statements in Appendix F, Part 1 and to apply these warning statements to the Schedule 2 pantoprazole entry under Appendix F, Part 3:

107. For short-term relief of minor and temporary ailments only; and

108. If symptoms persist beyond 7 days, recur or worsen, consult your pharmacist or doctor.

Substance summary

Pantoprazole is a Proton Pump Inhibitor (PPI). It inhibits specifically and dose proportionately H+/K+-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach. The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphonamide which binds to the H+/K+-ATPase, thus inhibiting the proton pump and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited. As with other PPIs and H2 receptor inhibitors, treatment with pantoprazole causes reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Scheduling status

Pantoprazole is currently listed in Schedule 3 and Schedule 4.

Schedule 4

PANTOPRAZOLE except when included in Schedule 3.

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'.

Scheduling history

The National Drugs & Poisons Schedule Committee (NDPSC), at its February 1995 meeting, noted that ADEC, at its 173rd meeting, had recommended approval for the registration of pantoprazole for the treatment of duodenal ulcer, gastric ulcer, reflux oesophagitis and gastrointestinal lesions refractory to H2-receptor antagonists. The Committee recommended a Schedule 4 entry.

In June 2005, the NDPSC agreed to include in Schedule 3 pantoprazole in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of GORD in packs containing not more than 14 days' supply. Members were convinced that the available efficacy and safety data supported an acceptable safety profile of pantoprazole 20 mg once daily for 14-day treatment consistent with S3 medicines. It was also agreed that the implementation date for this Decision would be 1 March 2006 to allow adequate time for collaboration with the pharmacy profession and the generation and provision of education materials and supply protocols for pharmacists to supply S3 pantoprazole appropriately. The Committee also agreed that the warning statements as proposed by the sponsor should be referred to the TGA's OTC Medicines Section for consideration of inclusion into the CMI and packaging for Somac Relief and the Required Advisory Statements for Medicine Labels (RASML) document. In addition, the matter relating to the wording of the indication in the proposed CMI should be referred to this Section. However, the Committee did not consider an Appendix H listing for pantoprazole as there was insufficient information available at the time to make an informed decision.

In October 2005, the NDPSC agreed to vary their pervious decision by delaying the implementation date for the rescheduling of oral pantoprazole 20mg to Schedule 3 to 1 May 2006 to allow the sponsor adequate time to develop pharmacist educational material.

Having regard to this advice, the NDPSC in February 2006, agreed to amend the implementation date for the oral pantoprazole Schedule 3 amendment to 1 May 2008 and to include this decision in the Gazette Notice and the Record of Reasons.

The NDPSC, in February 2009, reviewed the scheduling of the substance and agreed that the current scheduling of pantoprazole remained appropriate.

In February 2010, the NDPSC decided that the inclusion of pantoprazole in Appendix H was inappropriate.

In May 2012, after considering the ACMS's recommendation on the proposal to review the scheduling of the substance, the delegate made a final decision that the current scheduling of pantoprazole remains appropriate i.e. pantoprazole 20 mg, in packs containing no more than 14 tablets (equivalent to 14 day's supply) in Schedule 3.

Pre-meeting public submissions

Five public submissions were received.

Three public submissions did not support the proposal because: the 7-day pack did not provide optimal therapy and was therefore of limited benefit to consumers; the risks associated with prolonged use; and the need for consumers with gastrointestinal problems to seek professional advice to determine cause of their symptoms. The recommendations were that pantoprazole remain in S3 and that it also be listed in Appendix H.

One public submission recommended explicit labelling should pantoprazole be down scheduled to Schedule 2.

One public submission supported the proposal.

ACMS advice to the delegate

The ACMS recommended that 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.

The ACMS recommended an implementation date of 1 June 2015.

Delegate's interim decision

Delegate's interim decision was to:

- Include 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.
- Amend S3 and S4 entries for pantoprazole accordingly.
- Not include two new warning statements in Appendix F, Part 1 and to apply these warning statements to the Schedule 2 pantoprazole entry under Appendix F, Part 3:

  107. For short-term relief of minor and temporary ailments only; and

  108. If symptoms persist beyond 7 days, recur or worsen, consult your pharmacist or doctor.

The proposed implementation date was 1 June 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 a 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 the public health.

The reasons for the recommendation comprised the following:

- Short term use of pantoprazole for the treatment of heartburn and other symptoms of gastro-oesophageal reflux disease is likely to be safe and effective.
- Heartburn and other symptoms of gastro-oesophageal reflux disease are common. Other agents for the same indication are available as Schedule 2 medicines or are exempt from scheduling.

- All OTC proton pump inhibitor (PPI) medicines have similar efficacy and safety profiles. PPIs differ in this respect from many other pharmacological drug classes (such as H2-receptor antagonists or NSAIDs).
- Availability of a pharmacist would assist patients.
- The current RASML label warning statements for all OTC PPIs would apply to pantoprazole in Schedule 2 or Schedule 3.

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.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 2 - New entry

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 - Amended entry

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 - Amended entry

PANTOPRAZOLE except when included in Schedule 2 or 3.

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

1.9 CYCLIZINE

Scheduling proposal

The medicines scheduling delegate considered a proposal to amend the Schedule 3 entry for cyclizine for oral use to include a pack size limit of 10 tablets.

Substance summary

Cyclizine, a piperazine derivative, is a sedating antihistamine with antimuscarinic activity, although the sedative effects are not marked.

It is used as an antiemetic in the management of nausea and vomiting including motion sickness, postoperative nausea and vomiting, after radiotherapy, and in drug-induced nausea and vomiting. It is included as an antiemetic with some opioids, and in combination preparations for the treatment of migraine attacks. Cyclizine is also used for the symptomatic treatment of vertigo caused by Ménière's disease and other vestibular disturbances.

In the management of nausea and vomiting, cyclizine hydrochloride is given in a usual oral dose of 50 mg up to three times daily, although up to 200 mg may be given in 24 hours if necessary. For the prevention of motion sickness, the first dose should be given about 30 minutes before travelling.

Cyclizine is absorbed from the gastrointestinal tract and has an onset of action within 2 hours. The duration of action is reported to be about 4 hours. Cyclizine is metabolised in the liver to the relatively inactive metabolite, norcyclizine. Both cyclizine and norcyclizine have plasma elimination half-lives of 20 hours. Less than 1% of the total oral dose is eliminated in the urine in 24 hours.

Cyclizine tablets have been abused either alone or with opioids for their euphoric effects. They have been taken orally or used to make injections. It has been suggested that cyclizine dependence may occur when it is used with opioids in the treatment of chronic pain. Abuse of cyclizine has been reported in cancer patients receiving it by injection to control chemotherapy- or disease-related nausea (The Martindale 2014, viewed 29/08/2014).

Scheduling status

Cyclizine is currently listed in Schedule 3 and Schedule 4.

Schedule 3

CYCLIZINE in preparations for oral use.

Schedule 4

CYCLIZINE except when included in Schedule 3.

Scheduling history

The Poisons Schedule Sub-Committee Meeting in March 1966 considered the proposal that various preparations containing less than 2% antihistamines be exempt from Schedule 4 and included in Schedule 3. The committee re-affirmed its opinion that all antihistamines should be in Schedule 4 and noted its concern that motion sickness preparations are included in Schedule 3.

The committee recommended that the entry for antihistamines in Schedule 3 be amended to read:

"Antihistamines, all tertiary nitrogenous organic cases which possess pharmacological properties characteristic of antihistamine compounds in preparations labelled and packed for the treatment of motion sickness in packs of 10 does or less except meclizine, cyclizine and chlorcyclizine."

The committee recommended that the entry for antihistamines in Schedule 4 be amended to read:

"Antihistamines, all tertiary nitrogenous organic cases which possess pharmacological properties characteristic of antihistamine compounds in preparations labelled and packed for the treatment of motion sickness in packs of 10 does or less. This exemption does not apply to meclizine, cyclizine and chlorcyclizine."

The National Drugs and Poisons Schedule Committee (NDPSC) Meeting in February 2006 noted that travel sickness products containing a sedating antihistamine in S2 could be sold in premises licensed by the jurisdictions. It was noted that cyclizine for the treatment of travel sickness was reclassified from Pharmacy Only to Restricted Medicines in New Zealand as part of the rescheduling of single-active preparations containing sedating antihistamines and on the basis of its abuse potential.

There were no products containing cyclizine registered on the ARTG at the time and all cyclizine preparations were Prescription Only medicines in Australia. At the October 2005 NDPSC meeting it was agreed that it was appropriate to refer the scheduling of cyclizine to the February 2006 Trans-Tasman Harmonisation Working Party (TTHWP) meeting for initial consideration of harmonisation. The committee supported the option to retain all sedating antihistamines for travel sickness in S2 except for cyclizine and to reschedule it to S3 while retaining the primary entry in S4 to harmonise with New Zealand. The committee agreed that sedating antihistamines in small packs for use in the treatment or prevention of travel sickness remain in S2 except for cyclizine in oral preparations which the committee had agreed to include in S3 to harmonise with New Zealand.

Pre-meeting public submissions

No public submissions were received.

ACMS advice to the delegate

The ACMS recommended that the Schedule 3 entry for cyclizine be amended to specify divided preparations with a pack size limit of six dosage units.

The ACMS recommended an implementation date of 1 June 2015.

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

The reasons for the recommendation comprised the following:

- A maximum pack size of six dosage units is proposed for cyclizine in Schedule 3, due to the potential for abuse (and the recommended dosage and short-term duration of use). A six tablet pack is sufficient for the agreed dose for cyclizine HCl 50 mg tablets and the short term treatment of motion sickness. Inclusion of a pack size limit is consistent with requirements for pack size limits in the SUSMP for other OTC antihistamines for use for motion sickness, and in ARGOM for other OTC antihistamine products with abuse potential (Schedule 3 antihistamines indicated for use in insomnia). All these products are intended for short term use only.

- There are currently no registered Schedule 3 cyclizine preparations. The only cyclizine product currently on the ARTG is a Schedule 4 injection (for prevention of nausea and vomiting, post-operatively).
- Potential for adverse effects as a result of accumulation of cyclizine on repeated dosing (due to long half-life).
- Cyclizine in oral preparations is currently Schedule 3 (rather than Schedule 2, as for other antihistamines with antiemetic indications) due to its abuse potential. No history of abuse is noted in Australia (no oral cyclizine products are registered), but there have been reports of abuse of OTC cyclizine products by opiate users in New Zealand (tablets are dissolved in water and injected, usually with methadone), and reports of abuse of cyclizine by methadone users in the UK.
- The Schedule 3 entry should specify divided dose cyclizine preparations (for oral use). This would result in oral liquids being rescheduled to Schedule 4 - this is appropriate, as liquid cyclizine preparations present a greater risk of abuse than solid dose preparations, it would not affect any current products, and TGA has not considered any oral cyclizine product for use in children under 12 years.

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 3 entry for cyclizine to specify divided preparations with a pack size limit of six dosage units.

The proposed implementation date is 1 June 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 a substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of a substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; f) any other matters that the Secretary considers necessary to protect the public health.

Reasons for the decision are:

- Availability of OTC motion sickness products is appropriate however the risks of abuse or adverse events require restrictions on availability and pack size as OTC products.
- A maximum pack size of 6 dosage units is proposed for cyclizine in S3, due to the potential for abuse (and the recommended short-term duration use of up to 1 table three times a day for 48 hours). A 6 tablet pack is more than sufficient for the agreed dose for cyclizine 50 mg tablets.
- Inclusion of a pack size limit is consistent with requirements for pack size limits in the SUSMP for other OTC antihistamines for use for motion sickness, and in ARGOM for other OTC antihistamine products with abuse potential (S3 antihistamines indicated for use in insomnia). All these products are intended for short term use only.
- There currently are no registered S3 cyclizine preparations.
- The only cyclizine product on the ARTG is a S4 injection (for prevention of nausea & vomiting, post-operatively).
- Potential for adverse effects as a result of accumulation of cyclizine on repeated dosing (due to long half-life).

- Cyclizine in oral preparations is currently S3 (rather than S2, as for other antihistamines with antiemetic indications) due to its abuse potential.
- No history of abuse is noted in Australia (no oral cyclizine products are registered), but there have been reports of abuse of OTC cyclizine products by opiate users in New Zealand (tablets are dissolved in water and injected, usually with methadone); also reports of abuse of cyclizine by methadone users in the UK.
- The S3 entry should specify divided dose cyclizine preparations (for oral use). This would result in oral liquids being rescheduled to S4 - this would not affect any current products, and TGA has not considered any cyclizine product for use in children under 12 years.

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.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 3 - Amended entry

CYCLIZINE in divided preparations for oral use in primary packs containing 6 dosage units or less.

1.10 POMALIDOMIDE

Scheduling proposal

The medicines scheduling delegate considered a proposal to list pomalidomide in Appendix D Item 4, Appendix L, Part 2; and Appendix F, Part 3.

Substance summary

Pomalidomide is a derivative of thalidomide that has immunomodulatory and antiangiogenic properties. It is used with dexamethasone or as monotherapy for the treatment of multiple myeloma

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

in patients who have been treated with at least 2 other therapies including lenalidomide and bortezomib, and whose disease has progressed within 60 days of completing the last therapy. A usual oral dose of pomalidomide is 4 mg once daily taken on an empty stomach, for 21 days of a 28-day cycle.

Maximum serum concentrations of pomalidomide occur 2 to 3 hours after an oral dose. Plasma protein binding ranges from 12 to 44%. Pomalidomide is distributed into the semen. It is mainly metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4, with CYP2C19 and CYP2D6 playing a minor role. Pomalidomide is excreted via the kidneys with a plasma half-life of about 9.5 hours in healthy adults and 7.5 hours in those with multiple myeloma. About 73% of a dose was eliminated in the urine and 15% in the faeces, mainly as metabolites with a small portion as unchanged drug.

Because of its potential teratogenicity, pomalidomide use is restricted in women of child-bearing potential and similar precautions to thalidomide are required.

Pomalidomide is associated with haematological toxicity, particularly neutropenia, anaemia, and thrombocytopenia. Full blood counts should be monitored weekly for the first 8 weeks of treatment and then monthly thereafter; dose adjustments may be required. Venous thromboembolism has occurred during pomalidomide treatment, and prophylactic measures should be considered in those at increased risk.

Neuropathy, including peripheral neuropathy, has been reported with pomalidomide. Dizziness, confusion, anxiety, insomnia, and headache have occurred.

Other common adverse effects include fatigue, pyrexia, chills, gastrointestinal disorders, anorexia, changes in body weight, muscle spasm or weakness, arthralgia, pain including bone and muscle pain, dyspnoea, cough, epistaxis, hyperhidrosis, rash, dry skin, pruritus, electrolyte disturbances, hyperglycaemia, increases in blood creatinine, and renal failure. Vertigo, increases in bilirubin and hepatic enzymes, and interstitial lung disease have also occurred (Martindale 2014, viewed on 29 August 2014).

The mechanism of action of pomalidomide includes a variety of immunomodulatory effects such as induction of immune responses, enhancement of activity of immune cells, alteration and modulation of the induction of pro- and anti-inflammatory cytokines, and inhibition of inflammation. These compounds also have tumoricidal and anti-angiogenic activities that contribute to their anti-tumour activities.

The multiple pharmacological properties of pomalidomide suggest a potential therapeutic benefit in patients with multiple myeloma (MM). While it is structurally similar to both thalidomide and lenalidomide and shares a number of potentially therapeutic pharmacological properties, pomalidomide has a distinctly different activity and potency profile. It exhibits greater potency than thalidomide with regard to immune modulation, anti-inflammatory and anti-proliferative activity, and has greater potency than lenalidomide at anti-proliferative effects in MM cell lines, augmentation of CD4+ and CD8+ T cell proliferation, Th1 cytokine production and natural killer T cell activation. These differences allow the administration of pomalidomide at lower relative doses compared with thalidomide or lenalidomide.

In vitro and *in vivo* studies suggest that pomalidomide plus dexamethasone may be effective in MM resistant to lenalidomide/dexamethasone therapy. The mechanism underlying the synergistic responses is not fully understood.

Scheduling status

Pomalidomide is not currently scheduled in Australia or New Zealand. However, in 2013 pomalidomide was approved by the US Food and Drug Administration and the European Commission; and by Health Canada in 2014. In Canada the substance in contraindicated in pregnant women and women at risk of becoming pregnant and breast feeding women, while in the US only has the former contradiction. In the European Union, pomalidomide is contraindicated in females who are pregnant, and if used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be appraised of the potential hazard to the foetus.

Scheduling history

As pomalidomide has not been considered before, there is no scheduling history.

Pre-meeting public submissions

No public submissions were received.

ACMS advice to the delegate

The ACMS recommended that pomalidomide be included in Appendix D item 4; Appendix L, Part 2 with warning statements 7, 62 and 76; and Appendix F, part 3 with warning statements 7, 62 and 76 with an implementation date of 1 June 2015.

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

The reasons for the recommendation comprised the following:

- Known teratogen, Pregnancy Category X, similar pharmacological and toxicological profile to thalidomide therefore requires equivalent warning statements.
- Requires specialist oversight.
- Known teratogen, Pregnancy Category X.

Delegate's interim decision

The interim decision is to include Pomalidomide in:

- Appendix D item 4;
- Appendix L, Part 2 with warning statements 7, 62 and 76;
- Appendix F, part 3 with warning statements 7, 62 and 76.

The proposed implementation date is 1 June 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 a substance; b) the purposes for which a substance is to be used and the extent of use of a substance; and c) the toxicity of a substance.

Reasons for the decision are that:

- it is a known teratogen,
- it is Pregnancy Category X,

- it has similar pharmacological and toxicological profile to thalidomide therefore requires equivalent warning statements, and
- it requires specialist oversight.

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[10];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Appendix D, Item 4 - New entry

Poisons available only from or on the order of a specialist physician and for which the prescriber must, where the patient is a woman of child bearing age:

- Ensure that the possibility of pregnancy has been excluded prior to commencement of treatment; and
- Advises the patient to avoid becoming pregnant during or for a period of 1 month after completion of treatment.

POMALIDOMIDE

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

Appendix L, Part 2 - New entry

ADDITIONAL LABELLING REQUIREMENTS FOR CERTAIN HUMAN MEDICINES

Column 1 Poison	Column 2 Warning statements
Pomalidomide	7, 62, and 76

Appendix F, Part 3 - New entry

POISONS (other than agricultural and veterinary chemicals) TO BE LABELLED WITH WARNING STATEMENTS OR SAFETY DIRECTIONS

Poison	Warning statements	Safety direction
Pomalidomide	7, 62, and 76	

1.11 ENZALUTAMIDE

Scheduling proposal

The medicines scheduling delegate considered a proposal to list enzalutamide in Appendix D, Appendix L and Appendix F, Part 3.

Substance summary

Enzalutamide is a non-steroidal androgen receptor antagonist that blocks several steps in the androgen receptor signalling pathway binding to the androgen receptor, nuclear translocation of the activated receptor, and association of the translocated receptor with nuclear DNA. It is used in the treatment of metastatic castration-resistant prostate cancer in patients who have previously been treated with docetaxel. Enzalutamide itself is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19.

Scheduling status

Enzalutamide is not specifically scheduled.

Scheduling history

Enzalutamide has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

No public submissions were received.

ACMS advice to the delegate

The ACMS recommended that enzalutamide be included in Appendix L, Part 2 with warning statements 7, 67 and 87, in Appendix F, Part 3 also with warning states 7, 67 and 87 and in Appendix D, Item 6.

The ACMS recommended an implementation date of 1 June 2015.

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

The reasons for the recommendation comprised the following:

- Some efficacy in the treatment of metastatic castration-resistant prostate cancer.
- Use in or exposure of women of child-bearing age poses a significant threat.
- Treatment of metastatic castration-resistant prostate cancer.
- Not currently indicated for uses other than the treatment of prostate cancer.
- Teratogen.
- Does not appear to produce dependency.
- May be subject to extensions of indications or 'off-label' use in women.

Delegate's interim decision

The interim decision is include Enzalutamide in:

- Appendix D, Item 6;
- Appendix F, Part 3 with warning states 7, 67 and 87;
- Appendix L, Part 2 with warning statements 7, 67 and 87,

The proposed implementation date is 1 June 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 a substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of a substance; e) the potential for abuse of a substance; f) any other matters that the Secretary considers necessary to protect the public health.

Reasons for the decision are:

- it is a known teratogen,
- it is Pregnancy Category X,
- in the US it is contraindicated in women who are or may become pregnant,
- in Europe the Product Information states:

  4.6 Fertility, pregnancy and lactation - Women of childbearing potential. There are no human data on the use of Xtandi in pregnancy and this medicinal product is not for use in women of childbearing potential.

  Contraception in males and females - It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another

form of birth control must be used during and for 3 months after treatment. Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy - Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see sections 4.3 and 5.3).

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[11];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Appendix D, Item 6 - New entry

Poisons available only from or on the order of a specialist physician and for which the prescriber must, where the patient is a woman of child bearing age:

- Ensure that the possibility of pregnancy has been excluded prior to commencement of treatment; and
- Advises the patient to avoid becoming pregnant during or for a period of 3 months after completion of treatment.

ENZALUTAMIDE for human use

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

Appendix L, Part 2 - New entry

ADDITIONAL LABELLING REQUIREMENTS FOR CERTAIN HUMAN MEDICINES

Column 1 Poison	Column 2 Warning statements
Enzalutamide	7, 67 and 87

Appendix F, Part 3 - New entry

POISONS (other than agricultural and veterinary chemicals) TO BE LABELLED WITH WARNING STATEMENTS OR SAFETY DIRECTIONS

Poison	Warning statements	Safety direction
Enzalutamide	7, 67 and 87	

1.12 PONATINIB

Scheduling proposal

The medicines scheduling delegate considered a proposal to list ponatinib in Appendix D, Item 1.

Substance summary

Ponatinib is the active substance in an anticancer medicine. It is used to treat adults with the following types of leukaemia (cancer of the white blood cells):

- chronic myeloid leukaemia (CML);
- acute lymphoblastic leukaemia (ALL) in patients who are 'Philadelphia-chromosome positive' (Ph+).

Ponatinib is a BCR-ABL tyrosine kinase inhibitor that is used for the treatment of chronic, accelerated, or blast phase chronic myeloid leukaemia, or Philadelphia chromosome-positive acute lymphoblastic leukaemia, that is resistant to, or in patients who are intolerant of, prior tyrosine kinase inhibitor therapy.

Ponatinib is used in patients who do not respond to dasatinib or nilotinib (other medicines of the same class); or who cannot tolerate dasatinib or nilotinib and for whom subsequent treatment with imatinib (a third such medicine) is not considered appropriate. It is also used in patients who have a genetic mutation called 'T315I mutation' which makes them resistant to treatment with imatinib, dasatinib or nilotinib.

Scheduling status

Ponatinib is not specifically scheduled.

Scheduling history

Ponatinib has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

No public submissions were received.

ACMS advice to the delegate

The ACMS recommended that Ponatinib not be listed in Appendix D, Item 1.

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

The reasons for the recommendation comprised the following:

- Benefits: Treatment of chronic myeloid leukaemia and Philadelphia chromosome-positive acute lymphoblastic leukaemia.

  Risks: Life-threatening blood clots, severe occlusion of blood vessels, cardiac failure, pancreatitis and hepatotoxicity. Possible fetotoxicity.

- Purposes as above. Use is limited by the incidence of the diseases, adverse effects and cost.
- Attracts a FDA "black box" warning and a "risk evaluation and mitigation strategy" in view of the above risks.
- Oral tablets.
- The specialised nature of this drug is such that only haematologists are likely to use it.

Delegate's interim decision

The interim decision is to not include Ponatinib in Appendix D, Item 1.

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

Reasons for the decision are:

- Ponatinib will be prescribed by specialists only due to the nature of the disease being treated as well as the toxicity profile of the drug. It was very unlikely that GPs would prescribe Ponatinib.

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[12];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

2. Scheduling proposals referred to the Out of Session November 2014 meeting of the Advisory Committee on Medicines Scheduling

2.1 CANNABIDIOL

Scheduling proposal

To create a new Schedule 4 entry for cannabidiol for therapeutic use with consideration of an Appendix D listing.

Substance summary

Cannabidiol is a cannabinoid compound which occurs naturally in Cannabis sativa plants. Cannabidiol has the chemical formula C21H30O2 and its CAS number is 13956-29-1. The pharmacology of cannabidiol is complex and has been well characterised in in-vitro environments.

Some cannabinoid compounds work by binding to the CB1 and CB2 receptors in the brain. Cannabidiol does not activate CB1 and CB2 receptors directly however it has effects on many other 'signalling' systems and can be considered a 'multi-target' drug. Some of the effects of cannabidiol may be attributed to inhibition of the inactivation of endocannabinoids, such as anandamide. Other effects may be related to the chemical properties of the compound as opposed to pharmacodynamic effects. For example, it is thought that the presence of two hydroxyl groups enables cannabidiol to have an anti-oxidant action.

There is evidence that cannabidiol affects serotonin receptors (5HT1A), adenosine uptake, nuclear receptors of the peroxisome proliferator-activated receptors (PPAR) family and other pharmacological targets. Its pharmacological targets include receptors, ion channels, enzymes and cellular uptake processes.

There are reports that cannabidiol possesses antiproliferative, pro-apoptotic effects and inhibits cancer cell migration, adhesion and invasion. Evidence is also accumulating that there are positive effects of cannabidiol in the vasculature, where cannabidiol may induce vasorelaxation.

Information about the pharmacokinetics of the substance in humans is also accumulating.

Oral absorption is slow and unpredictable relative to other routes of administration, possibly due to the chemical's poor water solubility. There is significant first pass metabolism where the concentration of ingested cannabidiol is greatly reduced before it is absorbed into systemic

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

circulation, and the overall oral bioavailability may be as low as 6%. Other sources suggest oral bioavailability of between 12 and 19%. Oromucosal and sublingual delivery through sprays and lozenges results in less variability with similar overall bioavailability.

The distribution of cannabidiol is governed by its high lipophilicity and there is rapid distribution to the brain, adipose tissue and other organs. It is also highly protein bound.

Like most cannabinoids, cannabidiol is extensively metabolised in the liver by cytochrome P450 enzymes, predominantly the CYP3A and CYP2C series. The terminal half-life is estimated to be 18-32 hours, although earlier work suggested a much shorter half-life of only 9 hours.

Scheduling status

Cannabidiol is not currently specifically scheduled in the Poisons Standard.

As a constituent of cannabis, the substance would be captured by the entry for cannabis in Schedule 9.

However, cannabidiol may also be a constituent of hemp seed oil. Hemp seed oil is defined as the oil obtained by cold expression from the ripened fruits (seeds) of Cannabis sativa and is exempted from scheduling provided the oil contains 50 mg/kg or less of tetrahydrocannabinols and is labelled with the warning statement: “Not for internal use” or “Not to be taken”.

Cannabidiol is also mentioned in the Schedule 8 entry for nabiximols. However, nabiximols is defined as containing a range of cannabinoids including a mixture of both Δ9-tetrahydrocannabinol (THC) and cannabidiol.

Schedule 9

CANNABIS except:

(a) when separately specified in these Schedules; or
(b) processed hemp fibre containing 0.1 per cent or less of tetrahydrocannabinol and products manufactured from such fibre.

Schedule 9

TETRAHYDROCANNABINOLS and their alkyl homologues except:

(a) when separately specified in this Schedule;
(b) when included in Schedule 8;
(c) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with a warning statement:

Not for internal use; or

Not to be taken; or

(d) in products for purposes other than internal human use containing 50 mg/kg or less of tetrahydrocannabinols.

Schedule 8

DRONABINOL (delta-9-tetrahydrocannabinol) when prepared and packed for therapeutic use

NABILONE

NABIXIMOLS (botanical extract of Cannabis sativa which includes the following cannabinoids: tetrahydrocannabinol, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acid, tetrahydrocannabivarol, and cannabidivarol, where tetrahydrocannabinol and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray for human therapeutic use.

Scheduling history

Cannabidiol [CBD] has been discussed by the National Drug and Poisons Scheduling Committee (NDPSC) as a part of a consideration of tetrahydrocannabinols (THC) (February 2009) and the product Sativex© which lead to the creation of the nabiximols entry (June and October 2009).

While the focus of the February 2009 meeting item was on the classification of THC, a number of public submissions received were regarding the availability of Sativex© which contains both THC and CBD. At that time, jurisdictional members noted that it was difficult to give approval to SAS applications for medications containing CBD as it was considered a Schedule 9 substance, however access would be granted if CBD was placed in Schedule 8 for therapeutic use. This scheduling consideration was to be discussed at the June 2009 meeting.

Following further research regarding the Sativex© product, the NDPSC decided at the June meeting the Schedule 8 entry needed to exempt only the formulation from Schedule 9 rather than the "substance" and therefore created the Schedule 8 entry for CANNABIS SATIVA EXTRACT, listing the individual cannabidiols and restricting it's presentation to buccal sprays for therapeutic use.

In October 2009, the NDPSC considered the scheduling of nabiximols, after it was established that the US Adopted Names Council had designated 'nabiximols' as the approved non-proprietary name for an extract of Cannabis sativa containing, as major components, THC+CBD, and as minor components, related cannabinoids and non-cannabinoid components alpha- and trans-caryophyllenes i.e. the specific THC+CBD formulation considered appropriate for inclusion in Schedule 8 by the June 2009 meeting. The June 2008 cannabis sativa extract Schedule 8 entry was therefore amended to nabiximols.

Pre-meeting public submissions

Thirty-five submissions were received with 10 supporting the proposal, 8 with no comment on the proposal and 17 rejecting the proposal requesting that cannabis is scheduled instead. Of the 8 no comment submissions, a majority of those suggested the rescheduling of cannabis in Schedule 4.

ACMS advice to the delegate

The ACMS recommended that cannabidiol, including extracts of Cannabis sativa, and including preparations of up to 2% of cannabinoids, including cannabidivarin (CBDV), for therapeutic use, be included in Schedule 4.

The ACMS recommended an implementation date of 1 June 2015.

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

The reasons for the recommendation comprised the following:

- The condition that cannabidiol treats (the therapeutic use) requires diagnosis, management and monitoring under an appropriate medical practitioner.

- Cannabidiol has a safety profile which is consistent with a Schedule 4 listing.
- There is low risk of misuse or abuse as cannabidiol does not possess psychoactive properties.

Delegates' interim decision

The delegate's interim decision was:

- To include in Schedule 4:

  CANNABIDIOL in preparations for therapeutic use except when containing more than 2 per cent of other cannabinoids found in cannabis.

- To amend the Schedule 9 entry for TETRAHYDROCANNABINOLS and their alkyl homologues exception (b):

  – when included in Schedule 4 and Schedule 8

- The proposed implementation date was 1 June 2015.

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

The reasons for the recommendation comprised the following:

- The condition that cannabidiol treats (the therapeutic use) requires diagnosis, management and monitoring under an appropriate medical practitioner.
- Cannabidiol has a safety profile which is consistent with a Schedule 4 listing.
- There is low risk of misuse or abuse as cannabidiol does not possess psychoactive properties.
- The schedule entry needs to acknowledge that there is no pure form of cannabidiol currently available. However, low levels of impurities found in some cannabidiol products are not clinically significant and the scheduling entry should reflect this by allowing cannabinoids, up to 2 %.
- The entry allows for but does not specify any particular non-active cannabis impurity/ies to be within the up to 2%.
- The substances that comprise the up to 2% must be substances found in cannabis. They cannot be synthetic cannabinoids.
- The entry does not preclude the cannabidiol and/or any other cannabinoids being derived from natural sources or made artificially, consistent with the interpretation of the schedules.
- Appendix D is not supported as the criteria are not met. It is considered that it is the medical condition for which CBD may be used which requires treatment by a specialist. Cannabidiol, itself has no particular attributes that requires it to be included in Appendix D. Scope of practice will ensure the appropriate prescribing of cannabidiol rather than scheduling.

Delegates' considerations

The delegates 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[13];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

Delegates' final decision

The delegate has amended the scheduling entry from that published in the interim decision after further consultation with the jurisdictions to ensure clarity in the entry. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 4 - New entry

CANNABIDIOL in preparations for therapeutic use containing 2 per cent or less of other cannabinoids found in cannabis.

Schedule 9 - Amended entry

TETRAHYDROCANNABINOLS and their alkyl homologues except:

(a) when separately specified in this Schedule;
(b) when included in Schedule 4 or Schedule 8;
(c) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with a warning statement:

  – Not for internal use; or

  – Not to be taken; or

(d) in products for purposes other than internal human use containing 50 mg/kg or less of tetrahydrocannabinols.

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

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

3. New chemical entities - medicines for human therapeutic use

3.1 PEMBROLIZUMAB

Scheduling proposal

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

Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumour cells to overcome active T-cell immune surveillance.

Pembrolizumab is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults.

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

Scheduling status

Pembrolizumab is not specifically scheduled, but as it is a monoclonal antibody pembrolizumab is captured by monoclonal antibodies under Schedule 4. However, the delegate has decided to specifically list pembrolizumab in Schedule 4.

Pembrolizumab is not classified in New Zealand.

Delegate's consideration

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

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

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

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include pembrolizumab in Schedule 4, with an implementation date of 1 June 2015.

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

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

- It is a new chemical entity with no marketing experience in Australia.
- The benefit / risk profile has been considered in the evaluation of the NCE application.
- The proposed indication is: treatment of unresectable or metastatic melanoma in adults
- Toxicity has been considered in the benefit / risk evaluation of the NCE application
- Dosage, formulation, labelling, packaging and presentation have been considered in the benefit / risk evaluation of the NCE application.

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

Schedule entry

Schedule 4 - New entry

PEMBROLIZUMAB

3.2 LEDIPASVIR

Scheduling proposal

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

Ledipasvir is a new chemical entity and inhibits hepatitis C virus (HCV) replication through NS5A. It has a high potency and selectivity in multiple cell-based replicon assays and specificity exclusively for HCV.

Ledipasvir is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Ledipasvir is not specifically scheduled and is not captured by any entry in the Standard for the Uniform Scheduling of Medicines and Poisons No. 6.

Ledipasvir is not currently classified in New Zealand.

Delegate's consideration

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

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

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

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include ledipasvir in Schedule 4, with an implementation date of 1June 2015.

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

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

- It is a new chemical entity with no clinical/marketing experience in Australia.
- The fixed dose combination of ledipasvir and sofosbuvir is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.
- Reported adverse events from clinical trials include fatigue, headache, insomnia, nausea and arthralgia. Drug-drug interactions can occur when ledipasvir and sofosbuvir is co-administered with other medicines.
- Ledipasvir and Sofosbuvir, the fixed dose combination tablets should be prescribed by medical professionals who are familiar with the management of chronic liver diseases. The patients need to be instructed to follow the dosing regimens.

Schedule entry

Schedule 4 - New entry

LEDIPASVIR

3.3 ASUNAPREVIR

Scheduling proposal

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

Asunaprevir is an inhibitor of the NS3 serine protease of HCV, and subsequent viral RNA replication. Asunaprevir competitively inhibits the binding of substrate to NS3/4A protease complex, binding directly and reversibly to the protease, with Ki 0.24 to 1.0 nM, depending on the genotype strain employed.

Asunaprevir is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) in combination with:

- daclatasvir, an NS5A replication complex inhibitor, for patients with HCV genotype 1b infection.
- daclatasvir, peginterferon alfa, and ribavirin for patients with HCV genotype 1 or 4 infection.

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

Scheduling status

Asunaprevir is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* No. 6.

Asunaprevir is not classified in New Zealand.

Delegate's consideration

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

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

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

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include asunaprevir in Schedule 4, with an implementation date of 1 June 2015.

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

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

- It is a new chemical entity with no clinical and marketing experience in Australia.
- asunaprevir is indicated for the treatment of chronic hepatitis C virus infection in adults with compensated liver disease (including cirrhosis) in combination with:
  - daclatasvir,, an NS5A replication complex inhibitor, for patients with HCV genotype 1b
  - daclatasvir, peginterferon alfa, and ribavirin for patients with HCV genotype 1 or 4 infection.
- asunaprevir may cause liver toxicity. As asunaprevir is to be used in combination with other medicines, there could be adverse events caused by the concomitant medicines. Drug-drug interactions can occur when asunaprevir is co-administered with other medicines.
- Pregnancy category B1 is acceptable for asunaprevir. When used in combination with daclatasvir (B3), or daclatasvir and peginterferon alfa and ribavirin (category X), the most restrictive category is applicable.
- asunaprevir should be prescribed by medical professionals who are familiar with the management of chronic liver diseases. The patients need to be instructed to follow the recommended dosing regimens.

Schedule entry

Schedule 4 - New entry

ASUNAPREVIR

3.4 DACLATASVIR

Scheduling proposal

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

Daclatasvir is an inhibitor of the hepatitis C virus non-structural protein 5a (NS5A) replication complex. NS5A is a multifunctional protein with key functions in both HCV replication and modulation of cellular signalling pathways.

Daclatasvir is indicated, when in combination with other agents, for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis).

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

Scheduling status

Daclatasvir is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* No. 6.

Daclatasvir is not classified in New Zealand.

Delegate's consideration

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

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

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

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include daclatasvir in Schedule 4, with an implementation date of 1 June 2015.

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

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

- It is a new chemical entity with no clinical and marketing experience in Australia.
- Daclatasvir is indicated, in combination with other medicinal products, for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis).

- Daclatasvir is to be used for a medical condition (chronic hepatitis C virus infection) that requires careful diagnosis and management by medical professionals. Drug-drug interactions can occur when daclatasvir is co-administered with other medicines.
- Pregnancy Category B3 is proposed.
- There are side effects associated with the use of Daclatasvir, such as diarrhoea, nausea and headache, hypersensitivity reactions, drug-induced liver toxicity, etc.
- Daclatasvir should be prescribed by medical professionals who are familiar with the management of chronic liver diseases. The patients need to be instructed to follow the dosing regimens.

Schedule entry

Schedule 4 - New entry

DACLATASVIR