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

July 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 March 2014 meeting of the Advisory Committee on Medicines Scheduling (ACMS#11);
- 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 21 November 2013 and 30 January 2014 at: http://www.tga.gov.au/newsroom/consult-scheduling-acms-1403.htm and http://www.tga.gov.au/newsroom/consult-scheduling-accs-1403.htm, respectively. Edited versions of these submissions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Interim decisions

The delegate's interim decisions on recommendations by the ACMS#11 were published on **29 May 2014** at http://www.tga.gov.au/industry/scheduling-decisions-1405-interim.htm. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions.

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

Redacted versions of valid public submissions received in response to the interim decisions are available at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Final decisions

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either, confirming, varying or setting

aside the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling 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 Medicines and Chemicals* (SPF, 2010), available at http:www.tga.gov.au/industry/scheduling-spf.htm

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 http:www.tga.gov.au/industry/scheduling-poisons-standard.htm.

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

1. Scheduling proposals referred to the March 2014 meeting of the Advisory Committee on Medicines Scheduling (ACMS# 11)

1.1 DICLOFENAC

Scheduling proposal

The medicines scheduling delegate considered a proposal to amend the current Schedule 2 diclofenac entry to exempt dermal use preparations containing 2 per cent or less of diclofenac from scheduling. This would be more closely harmonised with its New Zealand medicine classification.

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

Substance details

Diclofenac, a phenylacetic acid derivative, is a cyclo-oxygenase inhibitor and used as a non-steroid anti-inflammatory drug (NSAID). It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions: musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

Diclofenac shows therapeutic efficacy by inhibiting a biochemical reaction path which is necessary for the biosynthesis of the pain inducer, prostaglandin. Diclofenac is an antifebrile, antipyretic and anti-inflammatory substance that is widely applicable in rheumatoid arthritis, osteoarthritis, spastic spondylitis, acute gout and inflammation or gout of lesion after operation. Administration via the transdermal route can by-pass the first pass metabolism. Transdermal delivery of diclofenac is reported to overcome all the problems of conventional dosage forms.

Scheduling status

Diclofenac is included in Schedules 2, 3 and 4, and Appendices F and H of the *Standard for Uniform Scheduling of Medicines and Poisons* (SUSMP), as follows:

Schedule 2

DICLOFENAC when:

(a) in divided preparations for oral use containing 12.5 mg or less of diclofenac per dosage unit in a pack containing 20 or less dosage units and labelled with a recommended daily dose of 75 mg or less of diclofenac;

(b) in preparations for dermal use containing 4 per cent or less of diclofenac except in preparations for dermal use containing 1 per cent or less of diclofenac or for the treatment of solar keratosis; or

(c) in transdermal preparations for topical use containing 140 mg or less of diclofenac.

Schedule 3

DICLOFENAC in divided preparations for oral use containing 25 mg or less of diclofenac per dosage unit in a pack containing 30 or less dosage units except when included in Schedule 2.

Schedule 4

DICLOFENAC except:

(a) when included in Schedule 2 or 3; or

(b) in preparations for dermal use unless:

(i) for the treatment of solar keratosis; or

(ii) containing more than 4 per cent of diclofenac.

Appendix F

Poisons	Warning statements	Safety direction
1. Diclofenac		101, 104

Appendix H

Schedule 3 Poisons Permitted to be Advertised.

Scheduling history

In March 1981, diclofenac was included in Schedule 4.

In February 1997, the National Drugs and Poisons Schedule Committee (NDPSC) rescheduled from Schedule 4 to Schedule 2, dermal preparations (creams) containing 1 per cent or less of diclofenac. This decision was based on the safety profile of a 1 per cent formulation and the then approved indications for use in readily recognised conditions (minor pain relief), which did not include treatment of solar keratosis.

In August 1999, the NDPSC decided that the scheduling of diclofenac in dermal preparations remained appropriate after considering recommendations from the Trans-Tasman Harmonisation Working Party to exempt diclofenac for dermal use.

In November 1999, the NDPSC deferred consideration of the scheduling of diclofenac in dermal preparations.

In February 2000, the NDPSC exempted dermal preparations of diclofenac from scheduling based on additional safety data.

In March 2011, following advice from the December 2010 ACMS meeting, the delegate included dermal preparations containing more than 1 per cent of diclofenac or preparations for the treatment of solar keratosis in Schedule 4.

In February 2012, following advice from the October 2011 ACMS meeting, the delegate rescheduled dermal preparations containing more than 1 per cent up to 4 per cent or less of diclofenac, except when for the treatment of solar keratosis, to Schedule 2. The delegate also confirmed that Schedule 4 remained appropriate for preparations containing more than 4 per cent of diclofenac, that preparations containing 1 per cent or less of diclofenac would remain unscheduled and that preparations for use in solar keratosis would remain Schedule 4.

In February 2013, following advice from the October 2012 ACMS meeting, the delegate included transdermal preparations for topical use containing 140 mg or less of diclofenac in Schedule 2, with an implementation date of 1 May 2013.

In a final decision published in June 2013, the delegate considered a proposal to exempt diclofenac when presented in a transdermal drug delivery system containing 140 mg or less of diclofenac. The decision was that the current scheduling was appropriate, as there was no clinical or marketing experience with this formulation in Australia and that Schedule 2 allows for access to professional advice at the time of purchase.

Public pre-meeting submissions

One submission supported the proposal as topical diclofenac has a favourable safety profile and a 2 per cent product would be a convenient addition to the products already available on the market. The submitter does not believe that the increased percentage of diclofenac would have a negative impact on consumer safety and that harmonisation would minimise consumer confusion.

The second submission did not support the scheduling proposal on the grounds that increasing the strength to double what is currently exempt from scheduling would pose a risk to public health. They stated that the safety profile of NSAIDs, of which diclofenac is one, requires the supply of higher strength topical preparations to be managed by the pharmacy sector. Furthermore, warning and direction labels do not address concerns of misuse by consumers with poor health literacy, which can be addressed by access to a pharmacist. The submitter also raised concerns regarding the consideration of rescheduling applications on the basis of harmonisation between countries and feels that scheduling should be determined "on best available evidence reflecting quality use of medicines, with harmonisation very much a secondary consideration".

ACMS advice to the delegate

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

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

The reasons for the recommendation comprised the following:

- Formulation has not been available for wider community use.
- Lack of evidence of safety from the wider use in the community.
- Different dosing regimen from the current product, therefore access from a pharmacist is appropriate.

Delegate's interim decision

The delegate's interim decision is that the current scheduling of diclofenac remains appropriate. The delegate is in agreement with the ACMS as to why the current scheduling of diclofenac remains appropriate and notes that a diclofenac 2 per cent topical solution is a prescription medicine in the United States of America.

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

The delegate's reasons for the decision are:

- Formulation has not been available for wider community use.
- Lack of evidence of safety from the wider use in the community.
- Different dosing regimen from the current product, therefore access from a pharmacist is appropriate.

Delegate's consideration

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]; and
- Other relevant information.

Submissions on the interim decision

One submission was received, providing further information addressing the delegate's reasons for the interim decision and requesting the delegate to reconsider their initial decision.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegate's final decision

The delegate notes the submission received in response to the 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, noting that it is the substance that is being scheduled, not a particular product and that similar overseas countries have it as pharmacy sale only e.g. Switzerland, United Kingdom, Ireland and Canada.

1.2 NAPROXEN

Scheduling proposal

The medicines scheduling delegate considered a proposal to amend the Schedule 2 entry for naproxen to include a modified release dosage form of 600 mg or less of naproxen per dosage unit in packs of 16 or less dosage units when labelled not for the treatment of children under 12 years of age.

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

Substance details

The chemical name of naproxen is (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid. Its molecular formula is $C_{14}H_{14}O_3$ 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

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

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 and in Schedule 2 and listed in Appendix F with warning statements 101 and 104.

Schedule 4

NAPROXEN except when included in Schedule 2.

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. 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 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 Schedule 3 and Schedule 4 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 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 220 mg 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. 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.

Public pre-meeting submissions

Four public pre-meeting submissions have been received. Two submissions support the scheduling proposal, with one submission providing evidence that the pharmacokinetic profile of the dosage form being considered as a part of this scheduling proposal is similar to products that meet the Schedule 2 naproxen listing. The other submission supported the proposal on the grounds that naproxen has as a well-documented safety profile, is safe for short-term use and has a low risk of inappropriate use. This submission also mentioned that a once daily dose would be considered a useful alternative to current multi dose products for consumers.

The other two submissions did not support the Schedule 2 proposal, instead suggesting that a Schedule 3 entry would be better suited for the proposal. Both highlighted that the proposal being considered more than doubles the amount of naproxen currently available without direct oversight from a health professional and that the use of naproxen can lead to a high risk of adverse gastrointestinal outcomes. The two submitters felt that health professional involvement should be required for a 600 mg of naproxen in a modified release dosage form product to ensure that consumers are well informed about the product. One submission noted that, as a Schedule 2 product, it could be sold in a non-pharmacy environment in a regional area where a pharmacist or health professional is not readily available, increasing the potential risk of adverse events.

ACMS advice to the delegate

The ACMS recommended that a new Schedule 3 entry for naproxen when in a modified release dosage form of 600 mg or less of naproxen per dosage unit in packs of 16 or less dosage units when labelled not for the treatment of children under 12 years of age and amend the current Schedule 4 entry. The committee also recommended to the delegate that the current Appendix F warning for naproxen should apply to this new dosage form.

The ACMS recommended an implementation date of 1 October 2014.

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

The reasons for the recommendation comprised the following:

- With the new dosage formulation there is a need for familiarity for both health practitioners and consumers particularly in view of the risk of use of multiple analgesics concurrently. Advice from the pharmacist is warranted at this stage.
- The advice of a pharmacist is necessary to ensure patients use the lowest effective dose for the shortest period of time.

Delegate's interim decision

The delegate's interim decision is that there be a new Schedule 3 for naproxen when in a modified release dosage form of 600 mg or less of naproxen per dosage unit in packs of 16 or less dosage units when labelled not for the treatment of children under 12 years of age and amend the current Schedule 4 entry. The interim decision also is that the current Appendix F warning for naproxen should apply to this new dosage form.

The interim decision is to have an implementation date of 1 October 2014

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

The reasons for the interim decision include those of the ACMS being:

- With the new dosage formulation there is a need for familiarity for both health practitioners and consumers particularly in view of the risk of use of multiple analgesics concurrently. Advice from the pharmacist is warranted at this stage.
- The advice of a pharmacist is necessary to ensure patients use the lowest effective dose for the shortest period of time.

Also 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.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Evaluation report (not publically available);
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[2]; and
- Other relevant information.

Submissions on interim decision

Three submissions were received. One submission supported the delegate's interim decision. Another submission maintained that a Schedule 2 entry would be appropriate and provided further evidence to support their claim. However, the submission did provide information in support of the delegate's interim decision. Like the second submission, the third also felt that the substance in this format could be placed in Schedule 2, however did accept the delegate's decision. All three submissions requested that the delegate consider including naproxen in Appendix H so that the extended release naproxen product may be advertised to the public.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegate's final decision

The delegate notes the submissions received in response to the 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 the implementation date of 1 October 2014 and that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 3 – New Entry

NAPROXEN in a modified release dosage form of 600 mg or less of naproxen 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 4 - Amendment

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

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

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]*.	-

1.3 PERAMPANEL

Scheduling proposal

The medicines scheduling delegate considered a proposal for a new Schedule 8 entry for perampanel and possible inclusion in Appendix D, Item 1.

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

Substance details

Perampanel is a first-in-class selective, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. It has been proposed for adjunctive treatment of partial-onset seizures.

Scheduling status

Perampanel is a new chemical entity and therefore it is not currently scheduled.

Scheduling history

Perampanel is a new chemical entity and therefore scheduling history is not available.

Public pre-meeting submissions

One submission was received, which did not support the scheduling proposal. The submission provided data which does not show a potential risk of abuse and dependency with perampanel. Therefore, the submitter states that the scheduling of the substance should be consistent with other anti-epileptic drugs (AEDs), which are classified as Schedule 4. A Schedule 4 entry for perampanel is consistent with the scheduling status in Europe, Canada and Switzerland. The submission also notes that a recent European Medicines Agency (EMA) Pharmacovigilance Risk Assessment

Committee (PRAC) report of 6 February 2014 concluded "that there is insufficient evidence for an association between Fycompa use and drug abuse, dependency and withdrawal".

ACMS advice to the delegate

The ACMS recommended that perampanel be included in Schedule 4 with an Appendix D, Item 5 entry, as well as an entry in Appendix K.

The ACMS recommended an implementation date of 1 October 2014.

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

- Benefits as an adjunctive treatment for seizures outweigh the risks.
- Medical diagnosis, management and monitoring are required.
- Close clinical monitoring is required. Toxicity is dose related. Potential for sedation.
- At therapeutic doses there is a moderate propensity for misuse, abuse or illicit use. Not dissimilar to other substances in Schedule 4.

Delegate's interim decision

The delegate's interim decision is that perampanel be included in Schedule 4 with an Appendix D, Item 5 entry, as well as an entry in Appendix K.

The interim decision is to have an implementation date of 1 October 2014.

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

Reasons for the interim decision include those from ACMS being:

- Benefits as an adjunctive treatment for seizures outweigh the risks.
- Medical diagnosis, management and monitoring are required.
- Close clinical monitoring is required. Toxicity is dose related. Potential for sedation.
- At therapeutic doses there is a moderate propensity for misuse, abuse or illicit use. Not dissimilar to other substances in Schedule 4.

As well as the following reasons:

- Consistency with other overseas jurisdictions including Europe.
- Little to no evidence regarding its abuse.
- An Appendix D Item 5 listing brings a further control beyond Schedule 4.
- Appendix K listing acknowledges the requirement for a sedation warning.

Delegate's consideration

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]; and
- Other relevant information.

Submissions on interim decision

No submissions on the interim decision were received.

Delegate's final decision

The delegate notes that no public submissions were received in response to the 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 the implementation date of 1 October 2014 and that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 4 – New Entry

PERAMPANEL.

Appendix D – New Entry

5. Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription).

PERAMPANEL for human use.

Appendix K – New Entry

Drugs required to be labelled with a sedation warning

PERAMPANEL

1.4 SODIUM OXYBATE

Scheduling proposal

The medicines scheduling delegate considered a proposal to include sodium oxybate for human therapeutic use in Schedule 8 and in Appendix D, Item 1.

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

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

Substance details

Sodium oxybate (Xyrem) is the sodium salt of gamma hydroxybutyrate (GHB) and is a central nervous system depressant that reduces daytime sleepiness and cataplexy in patients with narcolepsy. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $4H_7NaO_3$, and the molecular weight is 126.09 g/mole.

Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Each millilitre of Xyrem contains 0.5 g of sodium oxybate in USP Purified Water, neutralized to pH 7.5 with malic acid.

Scheduling status

Sodium oxybate is not specifically scheduled in the SUSMP. However, it is a derivate of the Schedule 9 entry for 4-hydroxybutanoic acid and its salts. The entry also includes the name GHB.

Scheduling history

In November 1991, Victoria Health wrote to the Drugs and Poisons Scheduling Sub-Committee (DPSSC) requesting that consideration be given to the scheduling of sodium oxybate (gamma hydroxybutyrate) after reports from the USA indicated potential for misuse and serious side effects. The committee felt that more information was required and sought further information from the Drugs of Dependence (DOD) branch, the TGA and State/Territory DPSSC members.

At the May 1992 meeting, the committee noted that gamma-hydroxybutyrate (sodium oxybate) was being used in conjunction with illicit amphetamines and being used as a substitute for anabolic steroids by the fitness/bodybuilding industry. It was also reported that GHB was being sold as 'Fantasy' in night clubs at $80 for 5 grams. As the substance had no approved therapeutic use or safety assessment, the committee felt that scheduling was not appropriate and suggested the DOD branch make the substance a prohibited import.

GHB was on the agenda again in November 1994, where the committee recommended the matter be referred to the Ministerial Committee on Drug Strategy, after it was noted that it was a substance of concern to the Australian Bureau of Criminal Intelligence because of substance related deaths in the USA.

According to the November 1996 meeting minutes, the committee approved an out of session Schedule 9 proposal for sodium oxybate, which was the new entry of 4-hydroxybutanoic acid. Concerns were raised that the entry may inadvertently capture derivatives that were not of concern. The committee decided to amend the entry so that salts of 4-hydroxybutanoic acid that could be subject to abuse were clearly captured by the entry.

In June 2002, when the committee considered gamma-butyrolactone (GBL) as a possible derivate of the GHB entry, the 4-hydroxybutanoic acid entry was reviewed. The outcome was that the current scheduling of 4-hydroxybutanoic acid is consistent with the committee's intent to exclude other derivatives of 4-hydroxybutanoic acid, except its salts, from the requirements of scheduling, as they are appropriately controlled through other State and Territory mechanisms. Therefore, GBL remained unscheduled.

While the scheduling of 4-hydroxybutanoic acid and it's salts was not reviewed in June of 2003, information was provided regarding the entry formed part of a consideration to schedule 1,4-butanediol and related analogues and metabolic precursors – mainly in relation to what substances are precursors/analogues to GHB and how they were currently being controlled.

Public pre-meeting submissions

Eleven pre-meeting submissions were received from the public. All were in favour of the decision to include sodium oxybate in Schedule 8, citing the potential health benefits it could bring to sufferers of narcolepsy and cataplexy. A majority of the submitters feel that the benefit of the substance outweighs the risks that sodium oxybate potentially poses. A number of the submissions outline side-effects and issues associated with current medication used to treat individuals who have been diagnosed with narcolepsy and cataplexy.

ACMS advice to the delegate

The ACMS recommended that sodium oxybate for human therapeutic use be included in Schedule 8 and in Appendix D, Item 1.

The ACMS recommended an implementation date of 1 October 2014.

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

The reasons for the recommendation comprised the following:

- Recognition of the therapeutic use warrants listing in Schedule 8 to enable prescription with appropriate supervision.

Delegate's interim decision

The interim decision is that sodium oxybate for human therapeutic use be included in Schedule 8 and in Appendix D, Item 1, with the Schedule 9 GHB entry amended accordingly.

The interim decision is to have an implementation date of 1 October 2014.

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

The reasons include:

- Sodium oxybate is currently available in the United States of America and in the European Union solely for the treatment of narcolepsy, sleep fragmentation and catalepsy.
- The product Xyrem is safe and efficacious at the therapeutic dose of 9 grams and when dispensed at its therapeutic dose, abuse of the substance is low.
- United Nations Convention on Psychotropic Substances made a decision to transfer GHB from Schedule IV to Schedule II of the 1971 Convention.
- Recognition of the therapeutic use warrants listing of Schedule 8 to enable prescription with appropriate supervision.
- Inclusion in Appendix D Item 1 provides further controls above those required for Schedule 8 medicines alone.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Evaluation report (not publically available);

- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[4]; and
- Other relevant information.

Submissions on interim decision

No submissions on the interim decision were received.

Delegate's final decision

The delegate notes that no public submissions were received in response to the 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 the implementation date of 1 October 2014 and that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 8 – New Entry

SODIUM OXYBATE for human therapeutic use.

Schedule 9 – Amendment

4-HYDROYXBUTANOIC ACID and its salts **except** for sodium oxybate when in Schedule 8. *(GAMMA HYDROXYBUTYRATE (GHB)).

Appendix D – New Entry

1. **Poisons available only from or on the prescription or order of an authorised medical practitioner.**

SODIUM OXYBATE for human use.

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

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

2. Agriculture and Veterinary Chemicals

2.1 HALAUXIFEN METHYL

Scheduling proposal

The chemicals scheduling delegate (the delegate) considered a proposal to include halauxifen methyl, also known as XDE-729 methyl, in Appendix B.

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

Scheduling status

Halauxifen methyl is not specifically scheduled.

Scheduling history

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

Substance summary

Halauxifen methyl is the first member of a new chemical class of synthetic auxin herbicides, the arylpicolinates. Halauxifen methyl mimics the effect of a persistent high dose of the natural plant hormone auxin, causing over-stimulation of specific auxin-regulated genes which result in the disruption of several growth processes in susceptible plants. Tissues that are undergoing active cell division and growth are particularly susceptible to injury[5].

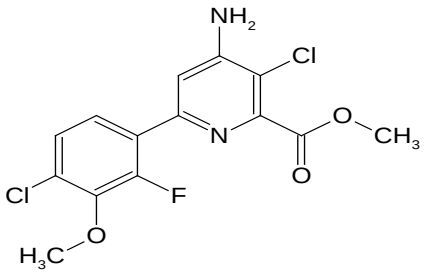

Figure 1. Structure of halauxifen-methyl

Note that halauxifen methyl hydrolysis into halauxifen acid as such the toxicity studies had been conducted using both substances. Toxicity information provided in this document is for halauxifen methyl and halauxifen acid and these have been specified appropriately.

Toxicity of the technical grade active constituent

The summary of acute toxicity studies is shown in the table below.

[5] Proposed Registration Decision PRD2014-12, Halauxifen-Methyl. Pest Management and Regulatory Agency, Health Canada. Available at [http://www.hc-sc.gc.ca/cps-spc/pest/part/consultations/_prd2014-12/prd2014-12-eng.php#s1]

Toxicity	Species	Halauxifen methyl	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	>5000 (one male died and no deaths for females)	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	>5000 (no deaths)	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Please see below	-	-
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	Non-irritant**	
Skin sensitisation	Local lymphnode assay	Non-sensitiser	

**SPF – Scheduling Policy Framework for Medicines and Chemicals (2010)*
*** halauxifen acid was a slight eye irritant.*

Regarding inhalational toxicity, the OCS indicated that waiver request by the applicant for the acute inhalation toxicity studies was accepted based on inability to generate a guideline-compliant respirable dry powder aerosol. The OCS indicated that the substance was not considered to be an acute inhalational hazard.

Repeat-dose toxicity potential

Short-term to chronic oral studies with mice, rats and dogs administered halauxifen acid demonstrated the kidney to be the target organ of toxicity with effects on urinalysis and clinical chemistry parameters and correlating histopathological changes including urinary bladder and renal tubules. These findings do not warrant scheduling.

Short-term to sub-chronic oral studies in rats with halauxifen methyl demonstrated that the most sensitive endpoint of toxicity was the liver, and was observed at doses lower than doses of halauxifen 9 acid causing kidney toxicity in short-term and sub-chronic studies in mice, rats and dogs.

Carcinogenic potential

Carcinogenicity studies in mice and rats with halauxifen acid did not reveal any treatment related neoplastic changes. Additionally, considering the above genotoxicity data and systemic toxicity data including mode of action (MOA) data and physiologically-based pharmacokinetic (PBPK) modelling, halauxifen methyl is not considered to be a carcinogenic hazard to humans.

Genotoxicity potential

Genotoxicity assays for gene mutation *in vitro* in bacterial cells and mammalian cells, and cytogenetic assays *in vitro* in rat and human peripheral lymphocytes were negative with and without metabolic activation for both halauxifen methyl and halauxifen acid. Additionally, an *in vivo* cytogenetic assay in mice peripheral erythrocytes with halauxifen acid was negative.

Developmental and reproductive toxicity potential

In developmental studies with halauxifen acid in rats and rabbits, foetotoxicity was only observed in rats (decreased foetal body weight and delayed ossification) at a maternotoxic dose of 526 mg/kg bw/d causing increase increased mortality, decreased gravid uterine weights, increased kidney weight, clinical signs, and decreased body weight gain and food consumption in dams, and is

considered a secondary non-specific consequence of such. In developmental studies in rabbits, no fetotoxcity was observed up to and including maternotoxic doses.

In developmental studies with halauxifen methyl in rats and rabbits, foetotoxicity was only observed in rabbits (decreased foetal body weight and delayed ossification of the pubis) and at the maternotoxic dose of 71.6 mg/kg bw/d causing liver toxicity, including histopathological changes in does, and was considered a secondary non-specific consequence of such.

Halauxifen acid was not a reproductive toxicant in a rat 2-generation study.

Neurological toxicity potential

Acute and subchronic neurotoxicity studies with halauxifen acid in rats did not reveal any neurobehavioural or neurohistopathological changes up to the highest dose tested.

Toxicity of the product

The summary of acute toxicity studies on the product is shown in the table below.

Toxicity	Species	Product	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	>5000 (females)	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	>5000 (both males and females)	Low toxicity
Acute inhalational toxicity LC_{50} (mg/L)	Rats	5.16 (both males and females)	Low toxicity
Skin irritation	Rabbits	Slight-irritant	
Eye irritation	Rabbits	Slight-irritant	
Skin sensitisation	Mice (local lymph node assay)	Sensitiser	

The OCS indicated that the product's slight skin and eye irritation and skin sensitisation potential was not considered to be due to halauxifen methyl but likely the product ingredients and the inclusion of a second active constituent, which is classified on Hazardous Substances Information System (HSIS) as a skin sensitiser.

Delegate's consideration

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

- evaluation report (not publically available);
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[6]; and
- other relevant information.

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

Delegate's final decision

Halauxifen methyl is a new type of auxin herbicide. The delegate notes that the toxicology profile is based mainly on studies with halauxifen acid, to which haluxifen methyl is rapidly hydrolysed during systemic absorption. Both compounds have a very low toxicity profile and do not satisfy any of the SPF factors for inclusion in any of the SUSMP schedules. Therefore the delegate has determined that halauxifen methyl does not require scheduling, and proposes to list halauxifen methyl in Appendix B. The implementation date is 1 October 2014.

Schedule entry

Appendix B – New Entry

Substance	Date of entry	Reason for listing	Area of use
HALAUXIFEN METHYL	October 2014	a. Low toxicity	1. Agricultural 1.1 Herbicide

2.2 IMEPITOIN

Scheduling proposal

The chemicals and medicines scheduling delegates (the delegates) considered a proposal to include imepitoin in Schedule 4.

The delegates decided to make a delegate-only decision. The joint committee of the Advisory Committee on Chemicals Scheduling (ACCS) & the Advisory Committee on Medicines (ACMS) was not consulted.

Scheduling status

Imepitoin is not specifically scheduled.

Other antiepileptic substances, including phenytoin (listed in Schedule 4 and Appendix F) and fosphenytoin (listed in Schedule 4) are listed in the SUSMP.

Scheduling history

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

The scheduling history of fosphenytoin is provided below.

In May 2000, the NDPSC decided to include fosphenytoin sodium in Schedule 4. This decision was based on the fact that the use of fosphenytoin sodium requires medical management.

In October 2006, the NDSPC decided to amend the fosphenytoin sodium entry to read fosphenytoin.

Substance summary

Imepitoin, is an anti-epileptic medicine. Epilepsy is caused by excessive electrical activity in the brain. Imepitoin partially activates the receptors for the neurotransmitter gamma-aminobutyric acid (GABA) in the brain. Neurotransmitters such as GABA are chemicals that allow nerve cells to communicate with each other. In the brain GABA is involved in reducing the electrical activity. By activating its receptors, imepitoin increases GABA's effects and helps to prevent seizures. Imepitoin also has a weak blocking effect on calcium channels. These are pores which let calcium

move into the nerve cells allowing electrical impulses to be transmitted between nerve cells. This may also help in controlling seizures[7].

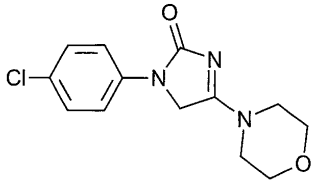

Figure 1. Structure of imepitoin

Acute toxicity of the technical grade active constituent

The acute toxicity end-points for the chemical are listed in the below table.

Toxicity	Species	Imepitoin	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	>2150	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Not provided	Not provided	
Eye irritation	Not provided	Not provided	
Skin sensitisation	Guinea pigs	Non-sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Repeat-dose toxicity

In a study, rats were administered gavage doses of 0, 31.6, 100 or 316 mg/kg bw/day imepitoin for 4 weeks. Additional animals were given the control and high dose for 4 weeks followed by a treatment-free period of 6 weeks. There was no treatment related mortality. Clinical signs were seen in rats given 100 mg/kg bw/day (coordination disturbances, sunken sides) and 316 mg/kg bw/day (hypokinesia, coordination defects, salivation, piloerection, stilted gait, sunken sides, full stomach, and emaciation). Reflexes, hearing, dental and ophthalmological examinations were unaffected. Food intake and body weight gains were depressed, erythrocyte counts, haemoglobin, haematocrit, triglycerides and total protein were decreased and reticulocytes, alanine aminotransferase, blood urea nitrogen, cholesterol and albumin:globulin ratio were increased in animals given 316 mg/kg bw/day. Urinalysis was similar between groups. Dilation of the heart was found in some animals in the high dose groups. The liver exhibited increased weight in males given 316 mg/kg bw/day and all treated female groups, marginal at the lowest dose. At the highest dose, hepatocellular hypertrophy was increased in incidence in females and in severity in males and cytoplasmic eosinophilia was observed. Adrenal weights were higher in males given 316 mg/kg bw/day and this was a reflection of the greater severity in cortical vacuolization in both sexes at this dose.

[7] Pexion – Imepitoin. European Medicines Agency. European Public Assessment Report summary for the public (2013). Available at [http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/veterinary/002543/WC500140843.pdf]

Mutagenicity

No information provided.

Genotoxicity

Imepitoin was not mutagenic or clastogenic in a range of genotoxicity assays.

Carcinogenicity

No information provided.

Reproduction and developmental toxicity

Atrophy of the testicular tubules, prostate, seminal vesicles, uterus and vagina were found in rats and atrophy of testicular tubules, Leydig cells and prostate were seen in dogs. The testicular effects were not reversible. The mechanism for these atrophic changes in reproductive tissues has not been investigated. Monkeys had no testicular toxicity. The findings in reproductive organs of rats and dogs suggested that imepitoin may have an impact on reproduction. Testicular tubular atrophy and the irreversible effects on sperm production would be expected to reduce fertility. The other atrophic changes in males and females could impair reproductive capacity and performance. Therefore, imepitoin should be regarded as possibly toxic to reproduction at the doses associated with toxicity in reproductive organs.

Developmental toxicity studies in rats and rabbits revealed increased embryotoxicity and retarded foetal development in both species, external and visceral foetal abnormalities in rats and skeletal variations in rats and rabbits. These findings were only apparent at doses associated with clinical signs and death or premature abortions in dams. The embryo and foetal toxicity was considered secondary to the severe maternal toxicity.

Acute toxicity of the product

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

The acute toxicity end-points for the product are listed in the below table.

Toxicity	Species	Imepitoin	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	>2150	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbits	Possible irritant	
Eye irritation	Rabbits	Possible irritant	
Skin sensitisation	Guinea pigs	Non-sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Observation in humans

A series of randomised, double-blind, placebo controlled Phase I studies was conducted in healthy male volunteers to investigate the pharmacokinetics of and the tolerance to imepitoin. A total of 124 subjects were enrolled in the 3 separate studies.

The administration of single oral doses of enteric coated capsules resulted in linear pharmacokinetics at doses of up to 300-400 mg. At higher doses, peak plasma levels were achieved slower, increases in concentration were sub-linear and increases in area under the curve (AUC) were supra-linear. The administration of a non-coated capsule gave a markedly higher maximum plasma concentration, but a similar AUC as compared to the same dose in coated form. In a multi-dosing experiment with 100-500 mg/kg dw/day, volunteers received non-coated capsules three times a day for up to 22 days. Maximum plasma levels and AUC were supra-linear. Plasma concentrations prior to dosing (trough levels) revealed accumulation of imepitoin following repeated exposure and showed that a steady state had been attained at day 7 or later.

In single oral doses of up to 800 mg, imepitoin was well tolerated in human subjects. Vertigo, fatigue, headache, disequilibrium, dizziness and nausea were reported in subjects treated with escalating doses of imepitoin (300 mg once on day 1, 300 mg three times/day on days 2-8, 400 mg three times/day on days 9-15, 500 mg three times/day on days 16-21 and then 500 mg once on the final day 22) and were considered possibly associated with treatment. Imepitoin, in oral doses of up to 500 mg three times a day was tolerated in human subjects with only minor adverse reactions.

Public exposure

The product will be administered to dogs by owners. Dermal exposure is likely through hand contact with the product formulation during administration. Oral exposure may occur as a result of hand to mouth transfer or the accidental direct ingestion of the product by a young child.

Contact with the hands is likely during normal use of the product. Skin contact will occur when the tablets are removed from the packaging and eye contact may occur as a transfer from hands. Acute toxicity following dermal doses and the extent of dermal absorption are not known. However, the small amounts on skin are not expected to lead to significant absorption and therefore are unlikely to pose a meaningful systemic risk. Skin sensitisation is not expected based on acute toxicity results. Slight skin and eye irritation are possible so label statements to avoid contact with eyes and to wash hands after using the product are required.

Contact with oral mucosa may occur through hand to mouth transfer. These amounts would be small and unlikely to result in significant exposure. A statement to wash hands after use would also mitigate the risk.

The most extreme situation in relation to oral exposure would be if a young child (weighing 10 kg) accidentally ingested a tablet. Such an event would not be expected to occur repeatedly so the risk will be determined against the potential effects of imepitoin following acute administration. The lowest acute oral no observed adverse effect levels (NOAEL) were 30 mg/kg bw in animals and 11 mg/kg bw in humans.

The intake of imepitoin and the margins of exposure (MOEs) for each product, calculated against this NOAEL, are given in the table.

Intakes of imepitoin and MOEs for a 10 kg child are provided in the below table.

Dose/Exposure	Product A	Product B
mg/kg bw	10	40
MOE versus animal NOAEL	3	nil
MOE versus human NOAEL	1	nil

The evaluator indicated that the above MOEs are unacceptable. It is clear that children must be denied access to product. The company has proposed that the product formulation will be packaged in high density polyethylene bottles with a polypropylene child-resistant tamper-proof closure which would limit the likelihood of access by children. The label statements required for a Schedule 4 substance will indicate the need to keep the products out of the reach of children. Imepitoin may also be reproductive toxicant. For these reasons a label statement indicating the products are harmful if swallowed would be appropriate.

International regulations

Imepitoin is licensed in the European Union for the treatment of canine idiopathic epilepsy.

Scheduling consideration

The delegates considered the following in regards to this application:

- evaluation report (not publically available);
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors[8]; and
- other relevant information.

Delegates' final decision

Imepitoin is a new benzodiazepine derivative with anti-epileptic properties. It is intended for administration by veterinarians for the control of epilepsy in dogs. It is a straightforward scheduling matter that imepitoin should be listed in Schedule 4, to enable appropriate clinical diagnosis and management of treatment. The toxicological and pharmacological profiles are consistent with other anti-epileptic medicines and there are no issues that would warrant additional controls via any other schedule. The issues raised in the evaluation report regarding appropriate label warning statements and packaging with child-resistant closures are a matter for the Australian Pesticide and Veterinary Medicines Authority (APVMA) and not a scheduling matter. The implementation date for this decision is 1 October 2014.

Schedule entry

Schedule 4 – New Entry

IMEPITOIN.

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

3. New chemical entities – medicines for human therapeutic use

3.1 INSULIN GLARGINE

Scheduling proposal

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

Insulin glargine is an insulin analogue.

Insulin glargine is indicated for once-daily subcutaneous administration in the treatment of type 1 diabetes mellitus in adults and children and type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia.

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

Insulin glargine is not specifically scheduled in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) but may be captured by the following group/class entry:

SCHEDULE 4

INSULINS.

Insulins are classified as a prescription medicine in New Zealand but not insulin glargine.

Delegate's consideration

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

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

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include insulin glargine in Schedule 4, with an implementation date of 1 October 2014.

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 of a substance.

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

- It is a new chemical entity and a biosimilar of insulin glargine with no clinical/marketing experience in Australia.
- Insulin glargine is an insulin analogue indicated for once-daily subcutaneous administration in the treatment of type 1 diabetes mellitus in adults and children and type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia.

- The toxicity profile of the substance meets the factors in the SPF for Schedule 4.
- The product contains an insulin glargine 100 IU/mL solution for injection presented as cartridges. The cartridges conventional glass cartridges, contain 3mL of injection solution, have a proposed 28 day open shelf life, and are supplied in packs of 1, 2, 5, and 10.
- Insulin glargine is an insulin analogue with a peakless glucose lowering profile and a prolonged duration of action that permits once daily dosing.
- The product containing insulin glargine is for individual patient use only, is given subcutaneously once a day and is not intended for intravenous administration.
- The substances does not appear to produce dependence.

Schedule entry

Schedule 4 – New Entry

INSULIN GLARGINE.

3.2 NALMAFENE

Scheduling proposal

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

Nalmafene is an opioid antagonist.

Nalmefene has been proposed for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high Drinking Risk Level (DRL), without physical withdrawal syndrome and who do not require immediate detoxification. The product should be prescribed in conjunction with psychosocial support focused on treatment adherence and reducing alcohol consumption.

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

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

Nalmafene is not classified in New Zealand.

Delegate's consideration

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

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

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include nalmafene in Schedule 4, with an implementation date of 1 October 2014.

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

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

- It is a new chemical entity with no clinical or marketing experience in Australia.
- The proposed indication requires that individuals taking nalmafene be under medical supervision.

Schedule entry

Schedule 4 – New Entry

NALMAFENE.