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

May 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 considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Matters not referred to an advisory committee

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

.

Table of contents

Glossary

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

Abbreviation	Name
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
HCN	Health Communication Network

Abbreviation	Name
INN	International Non-proprietary Name
ISO	International Standards Organization
LC50	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD50	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])

Abbreviation	Name
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
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities

Abbreviation	Name
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

Final decisions on matters not referred to an expert advisory committee

1. Chemicals

1.1 MAROPITANT

Scheduling proposal

The Chemicals and Medicines Scheduling Delegates (the delegates) considered a proposal to include in Schedule 5 tablet products containing maropitant for the treatment of motion sickness in dogs with a new reduced statement claims: 'For the prevention of vomiting due to motion sickness in dogs'. The proposal also requested that the current scheduling status be retained for all other maropitant containing products.

The delegates decided to make a delegate-only decision. Neither the Advisory Committee on Chemicals (ACCS) nor the Advisory Committee on Medicines Scheduling (ACMS) was consulted.

Scheduling status

Maropitant is listed in Schedule 4 in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Scheduling history

In June 2008, the National Drugs and Poisons Scheduling Committee (NDPSC) decided to include maropitant in Schedule 4 based on its toxicity profile.

Delegates' interim decision

Maropitant was included in Schedule 4 following consideration by the NDPSC in June 2008. The principal reasons for this decision were its toxicity profile and the need for veterinary diagnosis and supervision of treatment for emesis in dogs (including prophylactic treatment for motion sickness). The current submission seeks to re-schedule tablet products containing 16-160 mg of maropitant to Schedule 5, in packs of 4 tablets and labelled only for the prophylaxis of motion sickness, while retaining other tableted formulations and an injectable dose form in Schedule 4, for the original indications. Such a re-scheduling would allow easier access to the tableted medication for dog owners, but place greater responsibility on them for diagnosis and treatment of emesis associated with travel or motion.

The applicant has included 5 years of Periodic Safety Update Reports (PSUR) pharmacovigilance data following its introduction in Europe in 2006. These reports cover global adverse reactions reported in humans and in target animals (dogs and cats), segregated into reports addressing the injectable dose form and all tablets (16 to 160 mg) and treatment of emesis differentiated from the prophylactic treatment of motion sickness. These reports suggest a very low incidence of adverse reactions, although in some cases (e.g. emesis in dogs following treatment) they may represent a failure of treatment.

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

The delegates decided that the reasons for the interim decision comprise of the following:

- The low incidence of adverse effects reported in the PSUR is primarily associated with treatment supervised by veterinarians. The applicant provided information on the marketing status of maropitant in the 27 EU countries and 28 other countries where it is registered. None of these countries apparently allows an over-the-counter access, thus restricting supply to only veterinarians. It is possible that the incidence of adverse effects could rise if responsibility for diagnosis and monitoring of treatment falls outside the purview of professional veterinarians.

- Specific factors in this are that diagnosis of the causes of motion-related emesis is somewhat difficult and the occurrence of post-treatment emesis could encourage dog owners to make excessive treatment efforts to address perceived treatment failure. This could be exacerbated further by toxicology reports suggesting that maropitant can induce vomiting at doses only slightly higher than the recommended treatment dose.

- There are also recommendations that maropitant treatment is to be used with caution in dogs with liver disease, cardiac disease and in elderly dogs, with the potential for drug interactions with other drugs taken concomitantly.

- The dose recommended for prophylaxis of motion sickness is 8 mg/kg bw/d for up to two days. It therefore requires the dog owner to choose the correct product for their dog, in order to tailor the dose on a body weight basis, with the lower strength tablets for small dogs, and the higher strength tablets for progressively larger dogs. Such product choice could require professional advice.

- The APVMA did not support the re-scheduling of maropitant.

- On balance, the delegates consider that an insufficient case has been made to support the proposed re-scheduling, and have determined that maropitant should remain listed only in Schedule 4.

Applicant's response to delegates' interim decision

As the delegates' interim decision was not to amend the SUSMP in the manner set in the application, the applicant has been provided an opportunity to make a written submission on the delegates' interim decision.

The applicant indicated that for both the travelling dog and its owner, the ability to have access to the product without a veterinary consultation will ensure that product is more easily available to that consumer when needed. This level of benefit significantly outweighs the minimal risk that will exist if the particular use is allowed under Schedule 5.

The use of the product is not expected to be widespread under a Schedule 5 designation for this particular use. The reason for this is that at the current time, the use of the tablet formulation is very significantly lower than the injectable as used by veterinarians. Secondly, only a limited number of dogs are affected by motion sickness to the degree that vomiting is a significant issue. It is also expected that the moderately high price of the product will ensure that it is only used by consumers who have a major issue with vomiting due to motion sickness.

The applicant's responses to the specific issues raised by the delegates are:

- Regarding the delegates' concern that the low incidence of adverse effects reported in the PSUR, is primarily associated with treatment supervised by veterinarians, the applicant has indicated that the levels of human adverse events for this product are not due to the fact that it is prescribed or used under the supervision of a veterinarian, but because it is designed to be used in the home environment without veterinary supervision. Further, the interactions a veterinarian

has with their clients in the prescription of low risk products do not involve advice that would cause the potential for adverse events to be reduced. The low level of adverse events for the tablet formulation is because maropitant is inherently of low toxicity and the average consumer generally knows that 'medicines' should be treated with care.

- The delegates have indicated diagnosis of the causes of motion-related emesis is somewhat difficult. The applicant asserted that if a pet has a prior history of vomiting during a particular type of travel the product should be administered according to bodyweight, one hour prior to such travel. This product is not proposed to be registered such that it was necessary for a consumer to diagnose the vague premonitory signs of nausea due to motion sickness prior to administration, but simply to dose the animal prior to travel on a time based basis. This product has no claim for use during travel such that, in the event that nausea occurred on a particular trip, treatment would take place – rather it is a preventative product to be routinely administered prior to travel in dogs, which according to prior experience are likely to vomit. No monitoring is required after the dose has been administered.

- Regarding the delegates' concern that there are also recommendations that maropitant treatment is to be used with caution in dogs with liver disease, cardiac disease and in elderly dogs, the applicant has noted that the label statement adequately informs the end-user about the need for caution in such cases. The animal safety of the product has been adequately assessed by APVMA, and that human toxicity is likely to be extremely low based on the evidence submitted in relation to worldwide adverse events.

- It requires the dog owner to choose the correct product for their dog, to tailor the dose on a body weight basis. Such product choice could require professional advice. The application indicated that it agreed that it is necessary for an accurate determination of an animal's weight to allow safe and accurate dosing of the product. An appropriate label warning statement has been proposed to warn of this issue. Furthermore, most pet owners are extremely likely to have a local veterinarian who is likely to have weighed their dog as part of the dogs annual health check. For those pet owners who do not have access to a veterinary clinic, it is a simple matter to weigh their dog. The applicant asserted that a veterinary consultation is not required for a pet owner to determine the accurate weight of their dog and that weighing a dog is not an activity which is limited to the jurisdiction of a veterinarian.

Delegates' consideration

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

- the data package from the product sponsor, including pharmacovigilance data (not publicly available);
- the applicant's response to delegates' interim decision;
- scheduling application;
- section 52E of the Therapeutic Goods Act 1989;
- scheduling factors[1]; and
- other relevant information.

[1] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

Delegates' final decision

The delegates have confirmed the interim decision and the delegates decided that the reasons for the final decision comprise of the following:

The delegates have reviewed the applicant's response, noting that the arguments do not provide sufficient evidence to overturn the interim decision. The delegates still hold firmly to the view that management of treatment by a veterinarian is needed to provide correct product choice, to reinforce the need for adherence to dosage instructions and to ensure that a dog's health status does not compromise treatment with maropitant.

2. Medicines

2.1 3,4-DICHLORO-N-{[1- (DIMETHYLAMINO)CYCLOHEXYL]METHYL} BENZAMIDE (AH-7921)

Scheduling proposal

The medicines scheduling delegate considered a proposal to include the psychoactive substance AH-7921 in Schedule 9.

The reasons for the proposal were based on the following:

- Two deaths reported (one in Sweden, the other in the United Kingdom) attributed to AH-7921;
- Reports indicating an increased use of the substance in Australia through the monitoring of Australian internet forums; and
- Claims that the substance is an opiate and appears to have no legitimate therapeutic use.

The delegate has considered this matter as a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Substance details

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

Scheduling status

AH-7921 is not currently scheduled.

Scheduling history

As AH-7921 is not currently scheduled, there is no scheduling history available.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- the scheduling application;

- the European Monitoring Centre from Drugs and Drug Addition (EMCDDA) – Europol Joint report on AH-7921;
- section 52E of the Therapeutic Goods Act 1989;
- scheduling factors[2]; and
- other relevant information.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include 3,4-dichloro-N-{[1-(dimethylamino)cyclohexyl]methyl}benzamide (AH-7921) in Schedule 9, with an implementation date of 1 June 2014.

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

The delegate's reasons for the final decision were that AH-7921 is a synthetic opioid drug similar to morphine which has been available in EU since at least July 2012 and has been detected in 7 EU countries. It has been associated with 6 non-fatal intoxications and 15 deaths in three countries. AH-7921 has no currently established therapeutic value and it appears that the dangers are such to warrant limiting use to strictly controlled medical and scientific research. AH-7921 is likely to present a high risk of dependency, abuse and misuse. AH 7921 meets the factors for a Schedule 9 poison.

Scheduling entry

Schedule 9 – New Entry

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

2.2 ETHYL ALCOHOL

Scheduling proposal

The medicines scheduling delegate considered a proposal to reschedule ethyl alcohol from Appendix B to Schedule 3 for human therapeutic and cosmetic use.

The delegate has considered this matter as a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

Substance details

Ethyl alcohol can be produced through two manufacturing processes: either by the fermentation of carbohydrates or through the hydration of the substance ethylene.

Ethyl alcohol acts as a general Central Nervous System depressant, similar to volatile anaesthetic agents, producing the familiar effects of acute intoxication. Several cellular mechanisms are postulated: inhibition of calcium channel opening, enhancement of GABA action and inhibitory action at NMDA-type glutamate receptors.

Ethyl alcohol has a number of pharmaceutical applications such as, but not limited to, disinfection of skin, as a solvent and perseverative in pharmaceutical preparations, as a neurolytic, and as a

[2] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

sclerosant used for a variety of conditions including aldosterone-producing adenoma, parathyroid adenomas and gallbladder obstruction.

Outside of a pharmaceutical setting, ethyl alcohol is also contained in items for human consumption such as alcoholic beverages as well as motor and/or household fuels.

Scheduling status

Ethyl alcohol is currently listed in Appendix B - Substances considered not to require control by scheduling - of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). This exemption is for any use.

Scheduling history

The May 1974 Poisons Schedule Sub-Committee (PSSC) meeting was of the opinion that ethyl alcohol (then considered as ethanol) should be exempted from scheduling based on its toxicity data.

At the February 2003 meeting, the National Drugs and Poisons Schedule Committee (NDPSC) amended the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) to include Appendix B, replacing the previous 'Lists of Exemptions – Part 2' in the SUSDP. The NDPSC concluded that substances may be included in Appendix B because they have intrinsically low toxicity or where other factors suggest that the potential public health risk would be minimal.

In 2011, the delegate considered a proposal to reschedule ethyl alcohol from Appendix B to Schedule 9 for human consumption with the exception for use as a carrier and preservative in therapeutic tinctures or essences used in the preparation of food products. The delegate decided that the then current scheduling remained appropriate as ethyl alcohol for human consumption as a food or beverage were sufficiently controlled through separate legislation and regulatory bodies as to ensure the protection of public health. When the same proposal was re-submitted in 2012, the delegate's decision and reasons reflected those from 2011.

Delegate's consideration

The delegate considered the following in regards to this proposal:

- the scheduling application;
- the scheduling history of ethyl alcohol;
- the March 2011 and May 2012 final decisions requesting ethyl alcohol rescheduling;
- section 52E of the Therapeutic Goods Act 1989; and
- scheduling factors for inclusion in Schedule 3[3].

Delegate's final decision

The delegate made a final decision that the current scheduling exemption for ethyl alcohol through listing in Appendix B remains appropriate.

The delegate decided that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* include (a) risks and benefits of the substance, (b) purpose for which the substance is to be used, (c) toxicity, (d) presentation of the substance, (e) potential for abuse and (f) other matters considered necessary to protect public health.

The delegate's reasons for this interim decision included:

[3] Scheduling Policy Framework for Medicines and Chemicals <http://www.tga.gov.au/industry/scheduling-spf.htm>

- Although the submitted application did address matters under section 52E of the Act there was insufficient and relevant evidence to support a rescheduling proposal from Appendix B to Schedule 3 for human therapeutic and cosmetic use.

- The information provided in the application in regards to the risk to human health was in relation to human consumption of a food/beverage. The provisions of the SUSMP do not apply to food items and therefore scheduling for human consumption was not considered appropriate within the current regulatory system.

- Products containing ethyl alcohol for human consumption when presented as a food or beverage are subject to controls outside of scheduling. Restrictions associated with these products are controlled by regulatory bodies such as Food Standards Australia New Zealand and via specific Commonwealth and State and Territory legislation.

- Commonwealth and State and Territory regulatory bodies enforce such restrictions to ensure the protection of the public.

- There is little therapeutic or cosmetic use of ethyl alcohol and its major consumption is as a food which is not regulated by the TGA.

- Specific restrictions on non-food preparations containing ethyl alcohol are enforced by the relevant regulatory bodies (i.e. Therapeutic Goods Administration (TGA) for human therapeutic products and the Australian Pesticides and Veterinary Medicines Authority for agricultural and veterinary products).

- Should a product containing ethyl alcohol make therapeutic claims then it would be assessed by the TGA and the level of the therapeutic claims would determine how it would be assessed.

- There are already preparations containing ethyl alcohol included in the Australian Register of Therapeutic Goods and some of these are unscheduled over the counter preparations and this is considered appropriate.

- As described in the introduction to Appendix B, a factor when determining an Appendix B entry includes “the public access was limited such that scheduling was inappropriate or unnecessary”. In the case of ethyl alcohol there are other control mechanisms that limit its access for human consumption.