



Notice of interim decisions made under regulation 42ZCZN of the *Therapeutic Goods Regulations 1990*

6 June 2019

This web publication constitutes a notice for the purposes of regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (**Regulations**). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decisions made by a delegate of the Secretary under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee under subdivision 3D.2 of the Regulations in March 2019;
- the proposed date of effect of the proposed amendments (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to these interim decisions on or before 4 July 2019.

Persons making submissions are strongly encouraged to lodge submissions in an electronic format (word or unsecured PDF preferred) using the [public submission coversheet](#) available on the TGA's website. Where possible, submissions should be sent to the email addresses provided below:

- chemicals.scheduling@health.gov.au (for submissions relating to interim decisions made in relation to proposed amendments referred to the Advisory Committee on Chemicals Scheduling);
or
- medicines.scheduling@health.gov.au (for submissions relating to interim decisions made in relation to proposed amendments referred to the Advisory Committee on Medicines Scheduling or the Advisory Committee on Medicines and Chemicals Scheduling in joint session).

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received. The Secretary must not, however (pursuant to subregulation 42ZCZQ(5)), publish any information that the Secretary considers to be confidential information.

1 Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #26, March 2019)

1.1. Interim decision in relation to cetirizine

Interim decision:

For the reasons set out below, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision under regulation 42ZCZN not to amend the current Poisons Standard in relation to cetirizine.

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedule 4 and 2.

Reasons for interim decision:

I have made a decision that the scheduling of cetirizine remains appropriate under Schedule 4 and Schedule 2 and below I have set out my reasons. Among other things, the information I have considered is that increasing the general sales level pack size may delay a person seeking advice in a pharmacy therefore best practice treatment may be similarly delayed.

I am not persuaded by the evidence, supplied by the Applicant, that there is a public health benefit of increasing the pack size for cetirizine for the treatment of seasonal allergic rhinitis at the general sales level. The arguments made by the Applicant in this respect focus on accessibility, consumer convenience and affordability, and I am not satisfied that these factors would result in a public health benefit which outweighs my concerns regarding delaying seeking advice from a health professional. To the extent that the Applicant has submitted that benefits arising from accessibility, consumer convenience and affordability should be considered in a more general sense (beyond any effect on public health) this is not relevant to the matters which I must consider under section 52E of the *Therapeutic Goods Act 1989*. Accordingly, I have not given any weight to these matters (except insofar as they related to public health), and they were not material to my decision.

I find that the claims that Australia is somewhat conservative in terms of the pack size available at the general sales level compared to similar overseas regulators appear to be correct. On balance I consider that there are other differences in the way medicines are regulated that may influence safety and access to health professional advice. While risks associated with the proposed unscheduled 20 days' supply pack of cetirizine may potentially be no different to permitting multiple buys of smaller sizes, I have given substantial weight to the concern that increasing the pack size could lengthen the time before a consumer seeks advice from a pharmacist or other health professional. Having considered the evidence, it is my view that the potential negative consequences on quality use of medicines and overall best practice treatment of seasonal allergic rhinitis outweigh the risks.

I have considered the compelling evidence that cetirizine is well tolerated. However, as with other second generation antihistamines, its sedation effects are dose-related and risks can increase when taken in combination with alcohol and any other medication that can cause memory impairment and affect psychomotor skills. In addition, I note that in contrast to many other second-generation antihistamines, cetirizine crosses the blood-brain barrier. Having regarded for the sedation potential of cetirizine my view is that the current Appendix K entry remains appropriate.

I also concur with the committee's reasons under each matter relating to section 52E.

1.2. Interim decision in relation to glyceryl trinitrate

Interim decision:

For the reasons set out below, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision under regulation 42ZCZN to amend the current Poisons Standard in relation to glyceryl trinitrate as follows:

Appendix H – New Entry

GLYCERYL TRINITRATE.

INDEX – Amend Entry

GLYCERYL TRINITRATE

Schedule 4

Schedule 3

Appendix G

Appendix H

Proposed date of effect of the proposed amendment: 1 October 2019

Reasons for the interim decision (including findings on material questions of fact):

Having considered the matters set out in the [Guidelines for advertisements for medicines containing Schedule 3 substances](#) it is my view that GTN meets the criteria for advertising for the reasons set out below. While oral GTN is associated with significant adverse effects and requires caution for use, coupled with detailed advice about how to use it correctly, I have decided that adequate controls are already in place to manage these risks through the Schedule 3 listing and the need for pharmacist involvement in supply. I find that the ability to advertise this medicine should not change the medicine's risk profile and that any potential for inappropriate use will not be exacerbated by advertising.

In making my decision, among other things, I relied on evidence that there is a lack of safer alternatives and that GTN has a long history in the market place as a Schedule 3 medicine. Pharmacists will be aware of the sedating potential and potential drug interactions (e.g. PDE5 - sildenafil) that require increased patient education to ensure safe use so patient choice is unlikely to be adversely influenced by advertising. Any of the risks of potential abuse or misuse are low and further limited by sublingual GTN's propensity to cause vascular headaches, therefore it is unlikely that any risks associated with the dosage form that may impact on safe use would be exacerbated by advertising.

I considered the potential benefits to public health from advertising of this medicine, in particular:

- It could potentially raise awareness amongst people who have already been diagnosed with angina and prescribed GTN, of its availability over-the-counter to enable emergency supply;
- Public awareness amongst consumers that they can obtain repeat supplies from their pharmacist may help to ensure people have effective GTN supplies in their possession at all times, without them perceiving that they need to wait to obtain a script from their doctor;
- Oral sublingual GTN tablets have a short shelf life (i.e. 3 months from the date of opening the container) and advertising these products may assist in ensuring that angina sufferers have in date and active tablets;
- Advertising of topical GTN could encourage patients who have anal fissure to discuss their symptoms with a health professional, leading to better health outcomes.

I have taken into account the arguments in opposition of the proposed amendment, including that direct advertising to the public could divert patients from proper medical investigation. I find that on balance the public health benefits to be gained from inclusion of GTN in Appendix H outweigh the potential health risks, which in my view, are adequately controlled through the existing Schedule 3 listing.

1.3. Interim decision in relation to isosorbide dinitrate

Interim decision:

For the reasons set out below, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision under regulation 42ZCZN not to amend the current Poisons Standard in relation to isosorbide dinitrate.

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the matters under section 52E of the *Therapeutic Goods Act 1989* are not relevant to the decision regarding the inclusion of isosorbide dinitrate in Appendix H.

In my view, the relevant part of the SPF, 2018 is the section on the considerations for amending Appendix H, in particular, the [Guidelines for advertisements for medicines containing Schedule 3 substances](#).

Reasons for interim decision:

I have made the decision that isosorbide dinitrate should not be included in Appendix H of the Poisons Standard for the reasons set out below. In making my decision I have considered that there is potential for inappropriate use of isosorbide dinitrate which could be exacerbated by advertising.

Unlike glyceryl trinitrate, isosorbide dinitrate is not a first line treatment for angina. Dependence and tolerance can develop quickly with sustained use of isosorbide dinitrate and during sustained therapy, cross tolerance to other nitrate treatments may occur reducing their efficacy and, in terminating treatment, the dosage and frequency of administration must be gradually reduced to prevent potential withdrawal reactions such as increased frequency of angina attacks.

The advertising of isosorbide dinitrate may lead to erroneous requests for the substance from both patients with an angina diagnosis and patients without a proper diagnosis. Furthermore, there is potential for advertising to exacerbate this confusion by consumers with regards to appropriate treatment regimens for their condition. In my view, the risk that some patients may be supplied with isosorbide dinitrate incorrectly as treatment for angina at a pharmacy outweighs the benefits of a greater awareness of over-the counter access for patients through advertising.

In addition, I consider that there are additional risks associated with the dosage form of isosorbide dinitrate that could impact on its safe use. Both the 5mg sublingual tablet and the 10mg oral tablet are in Schedule 3; it is my view that there is a reasonable possibility that advertising may exacerbate confusion among consumers about which form/strength is taken orally and which is used sublingually.

Having considered the evidence, I have, in making my decision, relied on the evidence that isosorbide dinitrate is not a first line treatment for angina and it is not intended to treat acute angina episodes. The advertising of isosorbide dinitrate for angina treatment may result in some patients erroneously requesting this over other recommended treatment(s). Patients with angina should be under the treatment of a medical practitioner and will therefore be aware of the availability of isosorbide dinitrate treatment regimens if relevant to their condition.

1.4. Interim decision in relation to mometasone

Interim decision:

For the reasons set out below, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision under regulation 42ZCZN to amend the current Poisons Standard in relation to mometasone as follows:

Schedule 4

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

Schedule 2

MOMETASONE in aqueous nasal sprays delivering 50 micrograms or less of mometasone per actuation when the maximum recommended daily dose is no greater than 200 micrograms ~~for the~~ **and when packed in a primary pack containing 200 actuations or less, for the short term** prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years and over.

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MOMETASONE

Schedule 4

Schedule 2

Proposed date of effect of the proposed amendment: 1 October 2019

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are unable to be addressed for the purposes of amending the Schedule 4 entry for mometasone without clarification of the risk mitigation measures to support a Schedule 3 entry via Appendix M.

I agree with the committee's finding that the Schedule 2 entry for inhaled mometasone be amended as proposed by the Applicant. In addition, I agree with the Secretariat's proposed editorial change in the schedule order of the index entry.

In my view, the relevant parts of the SPF, 2018 are the sections on the Scheduling Factors for Schedules 4, 3, 2 and the considerations for amending Appendix H and M.

Reasons for interim decision:

I have made the decision to retain the current Schedule 4 entry for mometasone, and to amend the Schedule 2 entry for mometasone for the reasons set out below.

The change to the Schedule 2 entry for mometasone in aqueous nasal sprays to add 'when packed in a primary pack containing 200 actuations or less' was supported because prior to this change, there was no limit on the number of actuations supplied for treatment of up to six months. Whereas this amendment means that the Schedule 2 supply will have a limit requiring return of the patient to a pharmacy for resupply and possible consultation with a pharmacist. For the treatment of adults, the usual recommended dose for prophylaxis and treatment is two sprays (50 micrograms/spray) in each nostril once daily (total daily dose 200 micrograms). It is recommended that the dose is reduced to one spray in each nostril (total daily dose 100 micrograms) for maintenance treatment. A delivery device containing up to 200 actuations would permit fifty days of prophylaxis and treatment and/or 100 days of maintenance.

The basis on which I have decided to not down-schedule mometasone from Schedule 4 to Schedule 3 as proposed by the Applicant are as follows. Among other things, I consider the issues relevant to this

matter include that the diagnosis, management or monitoring of the medical condition is such that it requires medical intervention before the mometasone is used:

- consumers and/or pharmacists are not best placed to perform a differential diagnosis in the supply of mometasone (e.g. fungal infections, herpes zoster, infection);
- retention of mometasone in Schedule 4 will support better patient outcomes as any failures in the treatment of conditions with existing mild to moderate potency over-the-counter corticosteroids will be a signal that medical intervention is required;
- mometasone is classified as a Class III (potent) topical corticosteroid and there are systemic adverse events associated with medically unsupervised and inappropriate use; and
- inappropriate application of topical mometasone to the face can lead to significant skin problems including corticosteroid induced rosacea on the face (perioral dermatitis) and skin atrophy.

After taking into account the matters stated above, I find that the Scheduling Factors under Schedule 4 are met and that the existing Schedule 4 entry remains appropriate.

I am not sufficiently persuaded that the down-scheduling of mometasone will necessarily offer any additional benefit to the community given that existing provisions allow for 3 days emergency supply for a previously diagnosed condition in the absence of a prescription at the time of supply. From my understanding of the data, the mild corticosteroids in Schedules 2 and 3 appear to be supplied and used appropriately. I have not identified evidence from either pharmacists or consumers of any demand for, or unmet need for, a higher potency corticosteroid to be available without prescription. While *'0.1 per cent or less of mometasone in packs containing 15 g or less'* may possibly meet the Scheduling Factors for a Schedule 3 medicine, on balance, I consider the caveats to be too substantial, especially in the absence of clarification of the risk mitigation measures, to support a Schedule 3 entry. For the reasons referred to above, I have decided to retain the current Schedule 4 entry for mometasone.

From my reading of the application it was unclear what additional conditions or controls would be included in Appendix M that would support the proposed down-scheduling to Schedule 3, as pharmacists are already familiar with corticosteroids. Clarification of the risk mitigation measures to support a Schedule 3 entry via Appendix M is required. In the absence of proposed additional controls or supply requirements which would support a Schedule 3 entry, I have decided that an entry for mometasone should not be included in Appendix M.

I have made the decision that mometasone should not be included in Appendix H of the Poisons Standard on the grounds that there is a long history of the over-the-counter availability of topical corticosteroids which the community is familiar with. In addition, it is my view that there may only be limited additional benefit from the advertising of a more potent option and the choice of agent is best managed through consultation with the pharmacist.

1.5. Interim decision in relation to paracetamol (modified release)

Interim decision:

For the reasons set out below, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision under regulation 42ZCZN to amend the current Poisons Standard in relation to paracetamol (modified release) as follows:

Schedule 4 – Proposed Amended Entry

PARACETAMOL:

- a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;
- b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;
- c) in ~~slow release~~ **modified release** tablets or capsules containing more than 665 mg paracetamol;
- d) in non-~~slow release~~ **modified release** tablets or capsules containing more than 500 mg paracetamol;
- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules **except** in schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules **except** when included in Schedule 2;
- h) for injection.

Schedule 3 – Proposed Amended Entry

PARACETAMOL:

- a) when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2; **or**
- b) **in modified release tablets or capsules containing 665 mg or less paracetamol.**

Schedule 2

PARACETAMOL for therapeutic use:

- a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or
- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or
- e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

- f) in other preparations **except**:
 - i) when included in Schedule 3 or 4; or
 - ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:
 - (A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules,
 - (B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
 - (C) not labelled for the treatment of children 6 years of age or less, and
 - (D) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin; or
 - iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:
 - (A) packed in blister or strip packaging or in a container with a child-resistant closure,
 - (B) in a primary pack containing not more than 20 tablets or capsules,
 - (C) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
 - (D) not labelled for the treatment of children 6 years of age or less, and
 - (E) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin.

Appendix F, Part 3

Warning statements: **97**(Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.) and/or **98** (Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.), **99** (If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.), **100** (Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.)

Appendix H

PARACETAMOL

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PARACETAMOL

cross reference: ASPIRIN, IBUPROFEN, METOCLOPRAMIDE, SALICYLAMIDE, CAFFEINE

Schedule 4

Schedule 3

Schedule 2

Appendix F, Part 3

Appendix H

Proposed date of effect of the proposed amendment: 1 October 2019

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the SPF, 2018 are the Scheduling Factors for Schedules 4, 3 and 2.

Reasons for interim decision:

I have made the decision to up-schedule paracetamol in modified release (MR) tablets or capsules containing 665 mg or less of paracetamol to Schedule 3. This will enable MR paracetamol-containing products to be available to the public from a pharmacist, without a prescription, for the reasons set out below.

In making my decision, I have taken into account the arguments made in the public submissions in opposition of the proposed up-scheduling of MR paracetamol including that, but not limited to;

- Australian overdose rates appear to be lower than those overseas;
- there will be disadvantage to those who use MR paracetamol at the moment for the management of osteoarthritis; and
- up-scheduling could divert people to opioids or other medicines.

Among other things I find that the complex and unpredictable pharmacokinetic profile of MR paracetamol following an overdose poses an unacceptable risk to the Australian population and that my concerns regarding the potential for abuse outweigh the arguments to retain the Schedule 2 entry.

I consider that MR paracetamol is substantially safe with pharmacist advice available to ensure quality use under a Schedule 3 classification. My view is that there is the potential for harm if it is used inappropriately, and on balance, I find that up-scheduling MR paracetamol products to Schedule 3 would allow for additional pharmacist oversight while retaining public access.

In making my decision I considered that the Scheduling Factor 2 for inclusion in Schedule 2 states that, '*The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low.*' I considered the compelling body of evidence, including data from the European Medicines Agency, that there is an increased risk of death or serious liver injury in people who overdose either deliberately or accidentally on MR paracetamol compared to immediate release paracetamol. In my deliberations I have given substantial weight to the evidence that the increased risk associated with MR paracetamol use, is linked to unpredictable levels and duration of paracetamol in the blood following an overdose with MR paracetamol. I have considered the view that treatment protocols in Australia may be more effective than the EU from which these data are based. Nonetheless I consider that there is insufficient evidence to show that treatment protocols sufficiently mitigate the risks associated with MR paracetamol use in Australia. In making my decision I have had regard for the higher strength of MR, unpredictable pharmacokinetics, potential pharmacobezoar¹ and that large pack size increase the risks associated with overdose with MR paracetamol. I have decided that there is reasonable evidence that the potential for harm from inappropriate use of MR Paracetamol is not low and that the Scheduling Factors for Schedule 2 are not met.

Having considered the evidence for harm, my view is that greater direct involvement of pharmacists in the sale of MR paracetamol if it were included in Schedule 3 may prevent unintentional overdose through consumer education. Up-scheduling is likely to reduce the risk of either inadvertent overdose (through consumers not understanding that the products are intended for a specific chronic condition,

¹ Bezoars comprised of medications occurring in a background of altered mobility or anatomy of the gastrointestinal track.
<https://www.ncbi.nlm.nih.gov/pubmed/8590522>

have a lower limit of number of tablets per day and do not exert their full effect as soon after dosing as immediate release paracetamol) and the more common deliberate overdose due to greater oversight of sales. Pharmacists would be able to exert some control over purchase for suspected problematic or inappropriate use.

I have made a decision that a pack size constraint is not required to support the proposed Schedule 3 entry. At the time of making my decision I considered that the increased involvement of pharmacists in sales may be effective in educating consumers and in providing a barrier to access for intentional self-harm.

I have considered the evidence that 'modified release' is the current correct pharmacokinetic term used in the Product Information for these products, and I find that the use of 'slow release' in the current Poisons Standard does not correctly describe the pharmacological action of this formulation of paracetamol. For the reasons referred to above, I have decided that the 'slow release' descriptor should be replaced with 'modified release' as proposed.

I also concur with the committee's reasons under each matter relating to section 52E.

2 Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #24, March 2019)

2.1. Interim decision in relation to Polymer in Durazane 1500

Interim decision:

Pursuant to regulation 42ZCZN of the Regulations, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in regards to Polymer in Durazane 1500. The delegate of the Secretary made the decision to use the chemical names, cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes, in the Poisons Standard as follows:

Schedule 7 – New Entry

cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes **except when included in Schedule 6.**

Schedule 6 – New Entry

cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes **when presented in a wipe and when packaged in a container with a child-resistant closure, with chemical resistant gloves and labelled with the words “Do not use without protective gloves. Keep out of eyes”.**

Appendix E, Part 2 - New Entry

cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes
Standard statements: **A** (For advice, contact a Poisons Information Centre [e.g. phone Australia 13 11 26; New Zealand 0800 764 766] or a doctor [at once]; **E2** (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre [e.g. phone Australia 13 11 26; New Zealand 0800 764 766] or a doctor, or for at least 15 minutes.); **S1** (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.)

Appendix F, Part 3 – New Entry

cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes

Warning Statements: **2** (Corrosive); **10** (May produce severe burns); **78** (Attacks skin and eyes).

Safety directions: **1** (Avoid contact with eyes); **4** (Avoid contact with skin); **5** (Wear protective gloves when mixing or using.) **35** (Wash gloves thoroughly, immediately after use.)

Index – New Entry

cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes

Schedule 7

Schedule 6

Appendix E, Part 2

Appendix F, Part 3

In addition a new listing should be created in Part 2 – Control on medicines and poisons, section 2.4 – child-resistant closures as follows:

cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes **when included in Schedule 6, when presented in a wipe**

Nominal capacity: All sizes

Proposed date of effect of the proposed amendment: 1 October 2019

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

In my view, the relevant parts of the SPF, 2018 are the Scheduling Factors for Schedules 7 and 6, and the considerations for amending Appendix E and F.

Reasons for interim decision:

I find that it is inappropriate to use the proprietary name, Polymer in Durazane 1500, for the Poisons Standard entry as this would be inconsistent with current practice. Having considered the advice of the ACCS#24, I have decided that it is more appropriate to use the chemical name, cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes, in the Poisons Standard. The reasoning for my interim decision contained herein will refer to cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes, instead of Polymer in Durazane 1500.

I have made the decision to Schedule cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes in Schedules 7 and 6 of the Poisons Standard, below I will set out my reasons. I have taken into account the limited toxicological data on the substance provided by the Applicant and I note that this made performing a risk assessment difficult; there are no data on carcinogenicity, mutagenicity or sensitisation; and the genotoxicity data are insufficient. Nevertheless, based on my reading of the available data, the substance has a GHS of H314 (causes severe skin burns and eye damage) classification, and it is on these grounds, that I have determined the substance meets the Scheduling Factors for Schedule 7 in the SPF, 2018.

It is my view that reasonably foreseeable harm to users can be sufficiently reduced such that a Schedule 6 classification is appropriate for the wipes; while the substance alone presents severe dermal and eye hazards from unprotected use, I have reviewed, among other things, the available information on the packaging and presentation of the commercial product. I find that the dangers of the substance are such that special precautions are required in its handling, use and sufficient labelling to identify the risks before it can be allowed onto the domestic market under, Schedule 6, these include but are not limited to:

- i) distinctive packaging to distinguish it from other domestic wipes used on a neonate or infant, or a cosmetic product for use on the face.
- ii) inclusion of warning labels that 1) gloves should be used; 2) gloves should be washed following use; and 3) to keep out of eyes; and
- iii) child-resistant packaging of the wipes.

There are a few issues in considering this matter that I took into consideration; I have not been provided with the details of the other product ingredients, the packaging of the commercial product could not be confirmed based on the information provided in the application, no data were provided to explain why nitrile gloves specifically should be used with the product in question, and the concern as to how likely consumers will re-use the protective gloves given that only one pair is supplied, leading to unprotected use for the remaining wipes and a significant risk of toxicity to consumers. On balance, taking into account the special precautions required in its handling, use and labelling I have decided that a Schedule 6 entry would be appropriate for wipes containing cyclosilazanes, di-Me, Me hydrogen, polymers with di-Me, Me hydrogen silazanes.

2.2. Interim decision in relation to N-methyl-2-pyrrolidone

Interim decision:

Pursuant to regulation 42ZCZN of the Regulations, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision not to amend the current Poisons Standard in relation to N-methyl-2-pyrrolidone.

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are unable to be satisfactorily addressed due to insufficient evidence provided by the Applicant.

Reasons for interim decision:

I have made an interim decision to refer the proposed amendment for further advice from the Joint Advisory Committee on Medicines and Chemicals Scheduling and request further evidence on the reproductive toxicity data from the Applicant for the reasons set out below. Having considered the Application, my view is that there is a large amount of uncertainty regarding the likely exposure to N-methyl-2-pyrrolidone. I find that the lack of evidence supplied by the Applicant made it challenging for me to ascertain the reasonable foreseeable harm to consumers and assess the health hazard potential from repeated use. It was difficult for me to address the matters under section 52E of the *Therapeutic Goods Act 1989*.

Below I will set out matters that raised concern in my consideration of the proposed amendment: From my reading, the evidence that N-methyl-2-pyrrolidone is used in cosmetics available on the Australian market is limited, and I note this is contrary to the suggestion made in the application it is likely to be in cosmetic products including mascara, skin moisturiser, hair colour stain removal solution and nail products. I note that an industry report submitted as part of one of the public submissions indicated that there is only one product containing N-methyl-2-pyrrolidone sold on the Australian market. Again, this is contrary to the evidence supplied in the application. I am concerned with the lack of evidence on the concentration data available for N-methyl-2-pyrrolidone in any cosmetic product and the level of exposure for consumers and the actual risk.

In relation to the quantitative risk assessment provided by the Applicant, while I accept that the methodology used was correct, in the absence of real concentration data, however, my view is that the assessment may have overestimated consumer usage data for N-methyl-2-pyrrolidone. It is my understanding that the findings of the assessment are underpinned by the assumption that, a consumer is using three products containing N-methyl-2-pyrrolidone simultaneously, which in my view, is an unlikely scenario.

I find that the summary of the reproductive and developmental toxicity data lacked support from individual studies, which would benefit from additional clarification from the Applicant.

I have considered the evidence in support of a Schedule 6 entry on the basis of use at less than 2 per cent concentration and a 25 per cent cut-off in other preparations involving non-cosmetic use. I also note that the use of the margin of exposure to develop cut-offs would be consistent with the approach undertaken by the European Scientific Committee on Consumer Safety, however, this consideration was not material to my decision making under the provisions under section 52E of the *Therapeutic Goods Act 1989*. I have considered that public submissions have requested that for consistency and clarity, it would be useful to include the exception for "cosmetic preparations containing less than 2 per cent of the chemical" in the Schedule 5 entry as well as the Schedule 6 entry.

In exercising my powers under the *Therapeutic Goods Act 1989* to amend the current Poisons Standard I must have regard for the provisions of section 52E of the Act. I find that, on the grounds that I am unable to satisfactorily address section 52E as a consequence of insufficient evidence as set out above, I have made the decision to seek further evidence from the Applicant to clarify the 52E reasons for their proposed amendment. In addition, having considered that there are medicines currently active on the Australian Register of Therapeutic Goods (ARTG) that contain N-methyl-2-pyrrolidone, I have decided to refer the matter to the Joint Advisory Committee on Medicines and Chemicals Scheduling for further advice and consideration of possible new evidence to be submitted by the Applicant.

2.3. Interim decision in relation to MCPB

Interim decision:

Pursuant to regulation 42ZCZN of the Regulations, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision not to amend the current Poisons Standard in relation to MCPB.

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the SPF, 2018 are the Scheduling Factors for Schedules 5 and 6.

Reasons for interim decision:

I have made an interim decision to not to amend the current Poisons Standard in relation to MCPB for the reasons set out below. Taking into account that the current schedule for MCPB applies to MCPB and its salts and derivatives, where the salts or derivatives are known to have different human health risk profile to the parent compound, I find it appropriate that a separate schedule entry be designated. Having considered that, Schedule 6 substances have a moderate to high toxicity, such that eye irritation is severe (SPF, 2018), I find that on balance the lack of information on the formulations used in testing the salts for eye irritation supplied by the Applicant made it difficult to determine if eye damage can solely be attributed to the salts. The toxicological summary states 'The product is damaging to the eye'. It is my understanding however that the formulation contains the actives as dimethylamine salt and a surfactant, where both dimethylamine and the surfactant are known to cause serious damage to the eye. In making my decision to not amend the Poisons Standard I have given substantial weight to the data gap on the identity of the formulation in the eye irritation study and the relevance of the dimethylamine and surfactant to the observed eye damage and the absence of an independent assessor report in the application.

3 Interim decisions on a proposed amendment referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (ACCS/ACMS #21, March 2019)

3.1. Interim decision in relation to paracetamol

Interim decision:

Pursuant to regulation 42ZCZN of the Regulations, a delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to paracetamol as follows:

Schedule 4 – Amend Entry

PARACETAMOL:

- a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;
- b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;
- c) in slow release tablets or capsules containing more than 665 mg paracetamol;
- d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;
- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;
- h) for injection;
- i) **for the treatment of animals**

Schedule 3

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.

Schedule 2

PARACETAMOL for therapeutic use:

- a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or
- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or
- e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

- f) in other preparations **except**:
- i) when included in Schedule 3 or 4; or
 - ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:
 - (A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules,
 - (B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
 - (C) not labelled for the treatment of children 6 years of age or less, and
 - (D) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin; or
 - iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:
 - (A) packed in blister or strip packaging or in a container with a child-resistant closure,
 - (B) in a primary pack containing not more than 20 tablets or capsules,
 - (C) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
 - (D) not labelled for the treatment of children 6 years of age or less, and not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin

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PARACETAMOL

cross reference: ASPIRIN, IBUPROFEN, METOCLOPRAMIDE, SALICYLAMIDE, CAFFEINE

Schedule 4

Schedule 3

Schedule 2

Appendix F, Part 3

Appendix H

A new listing be created in Part 2 – Control on medicines and poisons, section 2.4 – child-resistant closures as follows:

Paracetamol included in Schedule 4, when packed and labelled for the treatment of animals

Nominal capacity: All sizes

Proposed date of effect of the proposed amendment: 1 October 2019

Reasons for the interim decision (including findings on material questions of fact):

I agree with the committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

In my view, the relevant parts of the SPF, 2018 are the Scheduling Factors under Schedule 6 and 4.

Reasons for interim decision:

I have made the decision to schedule paracetamol for animal use in Schedule 4 of the Poisons Standard to allow it to be made available with a prescription from a veterinary practitioner. In making my decision I have had regard to the Applicant's proposal for a Schedule 6 entry; the substance meets some of the criteria for Schedule 6 when used as intended, and I note that other concentrates for use in feed are Schedule 6. However, my view is that there is a moderate propensity for misuse, either accidentally carelessly or deliberately, making it unsuitable for a Schedule 6 classification. In my deliberations I have given substantial weight to the fact that the commercial animal product will contain large quantities of paracetamol, particularly in liquid form, and if the product is accidentally ingested or deliberately misused there is potential for significant human toxicity, including delayed irreversible hepatotoxicity. I considered that if listed as a Schedule 6 substance, a commercial product could be supplied to anyone aged 16 or over from any wholesale or retail outlet without veterinary oversight and advice on the serious risk of harm to humans. I am not persuaded that strong label warnings, extensive safety directions and child-resistant packaging under a Schedule 6 classification are sufficient to mitigate the risks associated with potential misuse. I consider it a reasonable possibility that consumers may not be aware of how highly concentrated the commercial product is and that even a small dose could be lethal, especially for a child. In the absence of professional guidance I have found that the liquid form, as proposed, is unsuitable for Schedule 6. It is my view that on balance a Schedule 6 classification is unsuitable due to the risks associated with misuse and the safety concerns inherent in the highly concentrated nature of the commercial product.

I will now set out my reasons to have paracetamol for animal use under a Schedule 4 classification. Among other things I have considered, including the information presented above on potential harm to humans, I have taken into account the potential adverse consequences for animals. It is my view that veterinary intervention is warranted as the presence of fever in pigs may be an indication of disease that requires other control measures e.g. identification of causative factors. In particular, additional biosecurity measures to control any outbreak, and protection from additional risk to the herd as well as neighbouring populations may need to be implemented. I have not given any weight to the first aid instructions and safety directions to be listed in the FAISD Handbook and required to appear on the product label, as determined by the APVMA evaluator, in the Human Health Risk Assessment Technical Report provided by the Applicant, as these matters are considered under other legislation at the time of making my decision.

In relation to the separate matter of paracetamol for human use; having reviewed the current Poisons Standard I have decided that a future delegate initiated application is appropriate to restrict the volume of liquid paracetamol available for human use in Schedule 2.