Australian Government
Department of Health
Therapeutic Goods Administration

Final decision and reasons for decision by a delegate of the Secretary to the Department of Health

16 May 2016

(ACMS meeting – November 2015)

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 delegate's 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 (the implementation date) of the decision.

The delegate's final decision and reasons relate to:

- A scheduling proposal for paracetamol/ibuprofen initially referred to the November 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS#16).

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 6 August 2015 on the TGA website at: Public notice about scheduling.

Redacted versions of public submissions received in response to the public notice will be published on or after the date of this notice at: Public submissions on scheduling matters.

Interim decisions

The delegate's interim decision and reasons for decisions on recommendations by the ACMS#16 were published on 3 February 2016 at https://www.tga.gov.au/scheduling-decision-interim/reasons-scheduling-delegates-interim-decision-and-invitation-further-comment-accs-and-acms-meetings-november-2015.

This public notice also invited further comment 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.

Edited versions of valid public submissions received in response to the interim decisions will be published at Public submissions on scheduling matters.

Final decisions

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

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the Scheduling Policy Framework for Chemicals and Medicines (SPF, 2015), available at SPF, February 2015.

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 the Federal Register of Legislation 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 the Federal Register of Legislation, is available at SUSMP.

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

1. Scheduling proposal referred to the November 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS#16)

1.1 Paracetamol/ibuprofen

Scheduling proposal

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

- To amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less.

Substance summary

The applicant has provided the following information regarding paracetamol/ibuprofen:

Paracetamol

Paracetamol is a *p*-aminophenol derivative, which has analgesic and antipyretic effects and weak anti-inflammatory activity. Paracetamol is given orally or as a rectal suppository for mild to moderate pain and for fever. It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever.

The usual oral dose of paracetamol in adults and children aged 12 years and older is 500 to 1000 mg every 4 to 6 hours as needed, up to a maximum of 4 g daily.

Paracetamol is in pregnancy category A.

Ibuprofen

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

Paracetamol and Ibuprofen

The Required Advisory Statements for Medicine Labels (RASML) requires that the labels of combination products include all the RASML statements that apply for each individual active ingredient. Therefore, the labels of OTC paracetamol/ ibuprofen combination products require the RASML statements that are required for scheduled paracetamol products and the RASML statements that are required for scheduled ibuprofen products.

Current scheduling status

Products containing paracetamol in combination with ibuprofen are currently included in Schedule 3 or 4.

Paracetamol in isolation is currently listed in Schedules 2, 3 and 4.

SCHEDULE 2 – current entry

PARACETAMOL for therapeutic use **except**:

a) when included in Schedule 4.

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

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

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

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

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

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

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

   ii) in a primary pack that contains not more than 20 tablets or capsules.

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

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

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

SCHEDULE 3 – current entry

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

SCHEDULE 4 – current entry

PARACETAMOL:

a) when combined with aspirin or salicylamide or any of their derivatives **except** when separately specified in the 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 or

f) for injection.

PARACETAMOL is also currently listed in Appendix F.

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

SCHEDULE 2 – current entry

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

a) in liquid preparations when sold in the manufacturer's original pack containing 8 grams or less of ibuprofen.

b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:

   i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent).

   ii) packed in blister or strip packaging or in a container with a child-resistant closure.

   iii) in a primary pack that contains not more than 25 dosage units.

   iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels.

   v) not labelled for the treatment of children 6 years of age or less, or

   vi) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

SCHEDULE 3 – current entry

IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled:

a) with a recommended daily dose of 1200 mg or less of ibuprofen.

b) not for the treatment of children under 12 years of age, **except** when included in or expressly excluded from Schedule 2.

SCHEDULE 4 – current entry

IBUPROFEN **except**:

a) when included in or expressly excluded from Schedule 2 or 3, or

b) in preparations for dermal use.

[Refer also to the Schedule 3 entry for Paracetamol, and to point (b) of the Schedule 4 entry for Paracetamol.]

IBUPROFEN is also currently listed in Appendix F.

Scheduling history

Paracetamol / ibuprofen combinations

National Drugs and Poisons Schedule Committee (NDPSC): June 2010

Delegate Final Decision: August 2010

The NDPSC considered the scheduling of paracetamol in combination with ibuprofen in June 2010. At that time, divided dose combinations containing up to 200 mg ibuprofen + 500 mg paracetamol were included in Schedule 2 (when labelled with a maximum daily dose of 1200 mg ibuprofen, and in packs of up to 100 dosage units). The NDPSC recommended, and the delegate confirmed, that the scheduling of ibuprofen and paracetamol that was current at that time remained appropriate.

Advisory Committee on Medicines Scheduling (ACMS): February 2011

Delegate Final Decision: June 2011

The ACMS considered a proposal from the Advisory Committee on Non-prescription Medicines (ACNM) that the delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination.

The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The delegate agreed with the ACMS advice.

Advisory Committee on Medicines Scheduling (ACMS): October 2012

Delegate Final Decision: February 2013

The ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less, and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The delegate agreed with the ACMS advice.

Pre-meeting public submissions

Five submissions were received.

Submissions supporting the proposal noted:

- Direct "to consumer" advertising of these combination products will be facilitated.
- The individual components have a long history of use and a well-documented, favourable safety profile.
- There is a public health benefit in consumer awareness of alternative options for relief of mild to moderate pain conditions.
- Unintentional overdose can be managed through product labelling and pharmacists being available at point of sale.
- There is little evidence of dependence, abuse, misuse or illicit use of the combination paracetamol and ibuprofen product.
- Combination products should only be indicated for children aged 12 years and up.
- Given the smaller pack size of combination products compared to single ingredient paracetamol and ibuprofen products, a potential benefit is that consumers will use less of these products over a shorter period of time.

- Pharmacy assistants are able to provide advice to consumers regarding the suitability and appropriateness of using a combination product and can refer to the pharmacist where required.

Submissions opposing the proposal noted:

- The use of paracetamol in combination with ibuprofen is not considered to be first-line therapy for the treatment of mild to moderate pain.
- A responsible quality use of medicines approach is to retain paracetamol–ibuprofen combinations in Schedule 3. This will facilitate a consistent environment where pharmacists can consider the most appropriate over-the-counter analgesic medicine (including consideration of paracetamol–ibuprofen combination products) and provide tailored advice for consumers.
- Delegate's reasons for not supporting Appendix H proposal for advertising Schedule 3 paracetamol/ibuprofen.
- Concerns regarding safety, particularly with respect to gastrointestinal bleeding and perhaps renal adverse effects.
- Pharmacists can recommend a paracetamol/ibuprofen combination product to consumers who request Schedule 3 CCA for pain relief. Rather than advertise to consumers, it is considered that paracetamol-ibuprofen combination analgesics products should be better promoted to pharmacists.
- Approving this scheduling proposal circumvents these concerns.
- Buying multiple small packs would not flag the need for pharmacist intervention.
- The proposed scheduling change would too easily result in inconsistencies and potential for abuse that is more than adequately catered for in the current scheduling.
- No new data is available in the published literature to revert the prior decision. The reasons for the prior rejections in relation to paracetamol/ibuprofen combination analgesics remain relevant and should be given due consideration in any decisions relating to the current application.

The public submissions are available at https://www.tga.gov.au/scheduling-delegates-decisions-public-submissions.

Summary of ACMS advice to the delegate

The ACMS recommended that paracetamol should be included in Schedule 2 when combined with ibuprofen, in packs containing 12 dosage units or less.

The committee recommended an implementation date of 1 June 2016.

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

The reasons for the recommendation comprised the following:

- The risk of adverse events as stated in the CCDS / PI documents are associated with the elderly and those with GI conditions e.g. ulcer, bleeding with previous NSAID use; cardiovascular conditions, renal insufficiency, hepatic failure, asthma/hypersensitivity. Also, there are risks associated with concomitant use of NSAIDs and other paracetamol products, as well as interactions with other drugs.

- These combination medicines have a low risk of diversion/abuse/addiction, and provide an effective option for short term use for moderate pain.
- The therapeutic indications include the temporary relief of acute (short term) pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches & pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, & aches and pains associated with colds & flu.
- Well established safety profile (as described in PSUR) – relating to the safety profile of each of the individual active ingredients.

Delegate's interim decision

The delegate's interim decision is amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less as per the below proposed wording for the schedule entries.

The Schedule 2 and Schedule 3 entries for paracetamol should be amended as follows:

Schedule 2 – Proposed Amendment

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 pack of not more than 3 day supply.

b) in other preparations **except**:

   i) when included in Schedule 4.

   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 phenylephrine and/or guaiphenesin 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.

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

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

      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 phenylephrine and/or guaiphenesin.

Schedule 3 – Proposed Amendment

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

The proposed implementation date is 1 June 2016.

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

The reasons for the recommendation comprised the following:

- Risks: Adverse events as stated in the CCDS / PI documents: mainly risks in the elderly, those with GI conditions e.g. ulcer, bleeding with previous NSAID use; cardiovascular conditions, renal insufficiency, hepatic failure, asthma/hypersensitivity. Also – concomitant use of NSAIDs & other paracetamol products, interactions with other drugs
- Benefits: Effective combination, low risk of diversion/abuse/addiction, provides an option for short term use for moderate pain; the combination itself uses lower doses of each active ingredient and also provides less IBU & paracetamol in each pack.
- Purposes and extent of use of the substance: - Temporary relief of acute (short term) pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches & pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, & aches and pains associated with colds & flu.
- Dose: Nuromol: 1 tablet three times / day (maximum 3 tablets/day as per labelling; PI not supplied by applicant however the CCDS was provided). In the UK, maximum daily dose is 6 tablets as the dose is 1-2 tablets three times/day; Maxigesic: 1-2 tablets every 6 hours (maximum 8 tablets/day). This represents a maximum of either 3 or 4 days' supply.
- Well established safety profile (as described in PSUR) – relating to the safety profile of each of the individual active ingredients.
- The following Australian registered products contain this combination:
  - Nuromol – AUST R 225322, Ibuprofen 200mg + Paracetamol 500 mg
  - Maxigesic – AUST R 218785, Ibuprofen 150mg + Paracetamol 500 mg
- 3 day supply considered appropriate for Schedule 2.
- No potential for diversion, addiction or illicit use.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

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

Public submissions on the interim decision

Four submissions were received. All supported the delegate's interim decision to amend the Schedule 2 entry, however 3 submissions requested an amendment to part (a) of the proposed entry into the Poisons Standard as follows:

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 of containing 12 dosage units or less.

Delegate's final decision

Following consideration of the submissions on the interim decision and the advice from the ACMS, the delegate has decided to vary the interim decision. In view of the dosage levels of paracetamol and ibuprofen the delegate considers it is more appropriate to limit the Schedule 2 entry to 12 dosage units per pack rather than 3 days' supply packs as this would ensure the total paracetamol available in the pack would not be excessive.

The final decision is to amend the paracetamol Schedule 2 entry to include the following:

> 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 not more than 12 dosage units per pack.

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

The reasons given by the delegate comprised the following:

- Risks: Adverse events as stated in the CCDS / PI documents: mainly risks in the elderly, those with GI conditions e.g. ulcer, bleeding with previous NSAID use; cardiovascular conditions, renal insufficiency, hepatic failure, asthma/hypersensitivity. Also – concomitant use of NSAIDs & other paracetamol products, interactions with other drugs.
- Benefits: Effective combination, low risk of diversion/abuse/addiction, provides an option for short term use for moderate pain, the combination itself uses similar doses of each active ingredient and also provides acceptable ibuprofen and paracetamol in each pack of 12 dosage units when compared with the unscheduled pack sizes for the single agents.
- Temporary relief of acute (short term) pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches & pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, & aches and pains associated with colds & flu.
- Well established safety profile (as described in PSUR) – relating to the safety profile of each of the individual active ingredients.
- A pack of 12 dosage units was considered appropriate for Schedule 2.

[1] Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

· No potential for diversion, addiction or illicit use.

The implementation date is 1 June 2016.

Schedule entry

Schedule 2 – Amend entry

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 not more than 12 dosage units per pack.

b) in other preparations **except**:

   i) when included in Schedule 3 or 4.

   ii) iin individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or 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.

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

Schedule 3 – Amend entry

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