Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

OTC medicine monograph: Paracetamol for oral use

Version 1.0, June 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission coversheet. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission coversheet.

Version history

Version	Description of change	Author	Effective date
V1.0	Original Publication	OTC Medicines Evaluation /OMA	18/06/13

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Introduction

This OTC Medicine Monograph outlines the requirements for Australian market authorisation of oral medicines containing paracetamol as a single active ingredient when applied for as an OTC New Product N2 application. Proposed products must comply with all aspects of the monograph relevant to their strength and dosage form to qualify for evaluation as an N2 application.

This monograph should be read in conjunction with the document Requirements for OTC new product N2 applications.

Active substance, dosage forms and strengths

Active substance

This monograph only applies to paracetamol (CAS No. 103-90-2).

Dosage forms and strengths

Acceptable dosage forms and strengths are shown in the table below.

Active substance	Dosage strengths	Dosage forms (excludes modified release dosage forms)
Paracetamol	250 mg	Soluble tablet
	500 mg	Tablet (including soluble or effervescent) Capsule
	500 mg	Oral powder
	600 mg	Oral powder
	1000 mg	Oral powder
	24 mg/mL (120 mg/5 mL)	Oral liquid or suspension
	48 mg/mL (240 mg/5 mL)	Oral liquid or suspension
	100 mg/mL	Oral liquid

Indications

Required therapeutic indications for inclusion in the Australian Register of Therapeutic Goods (ARTG)

Temporary relief of pain associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, arthritis, osteoarthritis, rheumatic pain, period pain, fibrositis, neuralgia, sore throat, tennis elbow, and colds and flu. Reduces fever.

For paediatric formulations, in addition to any of the indications above that are appropriate to the age group, the following indications would be acceptable: relief of pain associated with teething, earache and/or immunisation.

Label claims

All or some of the indications listed above may be included as label claims, as appropriate, depending on the intended age group. Terms should be exactly as specified above and qualified by the words “temporary relief of pain associated with...”.

Directions for use

Adults and children 12 years and over

Directions for use must be as shown in the table below.

Dosage form and strength	Single dose	Dose interval	Maximum daily dose
500 mg tablets, capsules, oral powder	1 – 2 tablets, capsules or sachets	every 4-6 hours, as necessary	8 tablets in 24 hours
600 mg oral powder	1 sachet	every 4-6 hours, as necessary	6 sachets in 24 hours
1000 mg oral powder	1 sachet	every 4-6 hours, as necessary	4 sachets in 24 hours

For soluble and effervescent tablets and oral powders, appropriate instructions for preparation of the dose form must be included.

Liquid dose products for children 1 month to 12 years

Dosages must be as shown in the table below.

Age	Average body weight (kg)	Single dose (mL) 24 mg/mL oral liquid	Single dose (mL) 48 mg/mL oral liquid	Single dose (mL) 100 mg/mL oral liquid
1 – 3 months	4 – 6	-	-	0.6 – 0.9 mL
3 – 6 months	6 – 8	-	-	0.9 – 1.2 mL
6 – 12 months	8 – 10	-	-	1.2 – 1.5 mL
1 – 2 years	10 – 12	6 – 8 mL	3 – 4 mL	1.5 – 1.8 mL
2 – 3 years	12 – 14	8 – 9 mL	4 mL	-
3 – 4 years	14 – 16	9 – 10 mL	4 – 5 mL	-
4 – 5 years	16 – 18	10 – 11 mL	5 – 6 mL	-
5 – 6 years	18 – 20	11 – 13 mL	6 mL	-
6 – 7 years	20 – 22	13 – 14 mL	6 – 7 mL	-
7 – 8 years	22 – 25	14 – 16 mL	7 – 8 mL	-
8 – 9 years	25 – 28	16 – 18 mL	8 – 9 mL	-
9 – 10 years	28 – 32	18 – 20 mL	9 – 10 mL	-
10 – 11 years	32 – 36	20 – 23 mL	10 – 11 mL	-
11 – 12 years	36 – 41	23 – 26 mL	11 – 13 mL	-

Doses should be given every 4-6 hours as necessary, with no more than four doses in 24 hours.

- Doses must be presented on the labels with ages (in months or years), weights (kg) and volumes (mL). Dosage instructions must also include advice consistent with the following:

  If you know that your child's weight is less than the weight corresponding to their age in the table, choose the dose for their weight.

- A product label could include only a subset of the age groups – for example, dosing for ages 1-5 years or 6-12 years only.

- Where dosage instructions for children under 6 months of age are included, the dosage instructions should clearly advise that the product only be given to this age group following the advice of a doctor.'
- Labels must state the maximum daily dose – for liquid preparations that include doses for more than one age group, this should be stated as: *Do not give more than 4 doses in 24 hours*.
- The dosage instructions must include the following statement:

  Do not give to children under x years [or months] (where 'x' years / months is the youngest age for which dosage instructions are included on the labels).
- For 100 mg/mL strength liquid products, a measuring device that can accurately deliver the required doses *must* be included - see Container/measuring device below.

Solid dose products for paediatric use

Solid dosage forms, strengths and dosages are acceptable for paediatric use only as specified in the table below.

Dosage form and strength	Age (years)	Average weight (kg)	Single dose (tablets)	Dose interval	Maximum daily dose
250 mg soluble tablets	2 – 3	12 – 14	½ – 1 tablet	every 4-6 hours, as necessary	4 doses in 24 hours
	3 – 7	14 – 22	1 tablet	every 4-6 hours, as necessary	4 doses (4 tablets) in 24 hours
	7 – 10	22 – 32	1 – 2 tablets	every 4-6 hours, as necessary	4 doses in 24 hours
	10 – 12	32 – 41	2 tablets	every 4-6 hours, as necessary	4 doses (8 tablets) in 24 hours
500 mg tablets/ capsules	7 – 12	22 – 41	½ – 1 tablet or 1 tablet* or 1 capsule	every 4-6 hours, as necessary	4 tablets/capsules in 24 hours

* 1 tablet single dose may be specified if the tablet is not divisible.

- Half tablet doses are only acceptable if tablets are scored and can appropriately deliver the intended dose (see Requirements for OTC new product N2 applications; Control of finished product).
- 250 mg soluble tablets with directions for use in children 12 years and under must include both ages and weights in the dosing instructions as above.

- For 500 mg tablets/capsules that include dosage for children aged 7-12 years, in addition to adults and children aged 12 years and over, average weight may be omitted from the dosage instructions.
- For soluble tablets, where more than one paediatric age group is specified, the maximum dose should be stated in numbers of tablets for each age group, or as *Do not give more than 4 doses in 24 hours*. For 500 mg tablets/capsules, the maximum paediatric dose should be specified in number of tablets/capsules (ie. 4 tablets in 24 hours).
- The dosage instructions must include the following statement:

  Do not give to children under x years (where 'x' years / months is the youngest age for which dosage instructions are included on the labels).

Labels

Labelling must comply with all relevant Australian requirements, as detailed in the document Requirements for OTC new product N2 applications, including all required warning statements.

Quality requirements

In addition to the quality requirements outlined in the document Requirements for OTC new product N2 applications, the following specific requirements apply to paracetamol monograph products:

Active premixes

Where paracetamol is sourced by the finished product manufacturer as part of an active premix, the finished product manufacturer must, as a minimum, control the premix for appearance/description, identification (one chromatographic and one non-chromatographic test), assay, related substances, residue on ignition or sulfated ash, and heavy metals. The limits applied should be taken from either the BP or USP monograph for paracetamol/acetaminophen (with all limits to be taken from the same monograph), adjusted where necessary to account for the presence of excipients in the mixture (for example, assay). Additional requirements in relation to active premixes are specified in the document Requirements for OTC new product N2 applications.

Finished product specifications

In addition to other requirements specified in the document Requirements for OTC new product N2 applications, the finished product specifications must comply, at a minimum, with one of the sets of requirements below, as relevant. The requirements below include all relevant BP general monograph/USP General Chapter requirements and TGO78 requirements. Further reference to these is not required.

1. The tests and limits in the **BP monograph *Paracetamol Tablets*** with the addition of:
   - tablet appearance
   - uniformity of dosage units (BP)
   - Test and limits for microbiological quality, in compliance with TGO 77
2. The tests and limits in the **BP monograph *Soluble Paracetamol Tablets*** with the addition of:
   - tablet appearance
   - uniformity of dosage units (BP)
   - dissolution (900 mL phosphate buffer pH 5.8, paddle at 50 rpm, NMT 70% after 45 minutes);
   - test and limits for microbiological quality, in compliance with TGO 77.
3. The tests and limits in the **BP monograph *Paracetamol Capsules*** with the addition of:
   - capsule appearance
   - uniformity of dosage units (BP)
   - test and limits for microbiological quality as required by USP, BP and Ph Eur and in compliance with TGO 77.
4. The tests and limits in the **BP monograph *Paracetamol Oral Suspension*** with the addition of:
   - suspension appearance
   - dissolution (900 mL phosphate buffer pH 5.8, paddle at 50 rpm, NMT 70% after 45 minutes);
   - content of 4′-chloroacetanilide[1] (NMT 10 ppm wrt paracetamol);
   - content of unspecified impurities[1] (any individual NMT 0.1% wrt paracetamol, total NMT 0.3% wrt paracetamol)
   - content of any preservatives included in the formulation;
   - test and limits for microbiological quality, in compliance with TGO 77.
5. The tests and limits in the **BP monograph *Paediatric Paracetamol Oral Suspension*** with the addition of:
   - suspension appearance
   - dissolution (900 mL phosphate buffer pH 5.8, paddle at 50 rpm, NMT 70% after 45 minutes);
   - content of any preservatives included in the formulation
   - test and limits for microbiological quality, in compliance with TGO 77.

[1] Assay methods specified for Paediatric Paracetamol Oral Suspension BP would be relevant. Alternative equivalent or superior methods could be used if appropriately validated.

6. The tests and limits in the **USP monograph *Acetaminophen Oral Suspension*** with the addition of:
   - suspension appearance
   - dissolution (900 mL phosphate buffer pH 5.8, paddle at 50 rpm, NMT 70% after 45 minutes)
   - content of 4'-chloroacetanilide[1] (NMT 10 ppm wrt paracetamol)
   - content of unspecified impurities[1] (any individual NMT 0.1% wrt paracetamol, total NMT 0.5% wrt paracetamol)
   - content of any preservatives included in the formulation
   - test and limits for microbiological quality, in compliance with TGO 77.
7. The tests and limits in the **BP monograph *Paediatric Paracetamol Oral Solution*** with the addition of:
   - solution appearance
   - content of 4'-chloroacetanilide[1] (NMT 10 ppm wrt paracetamol)
   - content of unspecified impurities[1] (any individual NMT 0.1% wrt paracetamol, total NMT 0.5% wrt paracetamol)
   - content of any preservatives included in the formulation
   - test and limits for microbiological quality, in compliance with TGO 77.
8. The tests and limits in the **USP monograph *Acetaminophen Oral Solution*** with the addition of:
   - solution appearance
   - content of 4-aminophenol[2] (NMT 0.5% wrt paracetamol)
   - content of 4'-chloroacetanilide[1] (NMT 10 ppm wrt paracetamol)
   - content of unspecified impurities[1] (any individual NMT 0.1% wrt paracetamol, total NMT 0.5% wrt paracetamol)
   - content of any preservatives included in the formulation.
   - test and limits for microbiological quality, in compliance with TGO 77.
9. For **powders for oral solution,** the following tests/limits:
   - powder appearance
   - solution appearance
   - identification (as for Paracetamol Tablets BP)
   - suitable test and limit for pH of solution
   - dissolution (using conditions and limits for Paracetamol Tablets BP)

[2] Assay method specified for Acetaminophen Oral Suspension USP or Paediatric Paracetamol Oral Suspension BP would be relevant. Alternative equivalent or superior method could be used if appropriately validated.

- uniformity of dosage units (BP)
- assay[3] (90.0-110.0% LC)
- test and limits for impurities (as for Paracetamol Tablets BP)
- test and limits for microbiological quality, in compliance with TGO 77.

Container/measuring device

- Paracetamol products must be sold in containers that comply with Therapeutic Goods Order No 80, Child Resistant Packaging Requirements for Medicines.
- If a measuring device is to be supplied with the product, calibrations must be exclusively in metric units and must allow all the doses shown on the labels to be measured accurately. Details of the calibrations on the measuring device must be provided with the submission (a sample may also be requested). Further considerations and requirements regarding measuring devices are detailed in *ARGOM Appendix 2 – Guidelines on quality aspects of OTC applications, Section 8: Finished product container*.

[3] Assay methods for Paracetamol Tablets BP or Acetaminophen Tablets USP would be relevant. Alternative equivalent or superior methods could be used if appropriately validated.

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Reference/Publication #