

5.17 MERCAPTOPURINE oral suspension 20 mg/mL, 100 mL; Allmercap®; Link Healthcare Pty Ltd.

1 Purpose of Application

- 1.1 The minor submission sought an Authority Required (Streamlined) listing for the treatment of acute lymphoblastic leukaemia in paediatric patients when the tablet form is unsuitable. A request for mercaptopurine oral suspension to be deemed an exempt item under subsection 101 (4AB) of the *National Health Act 1953* (the Act) was also made.

2 Background

- 2.1 Mercaptopurine oral liquid suspension was TGA registered on 16 June 2014 for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients.

- 2.2 Oral mercaptopurine is part of the standard chemotherapy for ALL and mercaptopurine 50 mg tablets (Purinethol®) have been on the PBS since the early 1960's. Mercaptopurine tablets are currently PBS-listed as an unrestricted benefit.

2.3 Subsection 101 (4AB) of the *National Health Act 1953* – exempt items

Subsection 101 (4AB) of the Act provides that the PBAC has the following function relating to a Ministerial determination about exempt items under Section 84AH of the Act:

If the Committee is of the opinion that the following circumstances exist in relation to a pharmaceutical item:

- (a) the listed drug in the pharmaceutical item represents suitable therapy for a particular patient population;
- (b) the pharmaceutical item is suitable for use by a particular subgroup of that population because of either or both of the form and manner of administration of the drug in the item;
- (c) no other pharmaceutical item that has that drug is suitable for use by that subgroup because of either or both of the form and manner of administration of the drug in that other item;

The Committee must advise the Minister that those circumstances exist in relation to the pharmaceutical item.

- 2.4 The intent of the Exempt Item provision is to provide exemptions for particular formulations of drugs (e.g. an oral suspension) used by a demographic subgroup (e.g. children or geriatric persons) for whom other formulations of that drug are not appropriate (e.g. because they cannot swallow tablets). The patient subgroups will be demographically based, not disease based.
- 2.5 A determination by the Minister that a pharmaceutical item is an exempt item would exempt the pharmaceutical item from statutory price reductions under PBS reform.

3 Requested Listing

3.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Proprietary Name and Manufacturer	
MERCAPTOPYRINE				
oral liquid suspension 20 mg/mL, 100 mL	1	2	Allmercap	LM

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Maintenance therapy
Severity:	---
Condition:	Paediatric acute lymphoblastic leukaemia
PBS Indication:	Paediatric acute lymphoblastic leukaemia
Treatment phase:	---
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have acute lymphoblastic leukaemia
Population criteria:	Patient must be paediatric AND the solid dose form of mercaptopurine must be unsuitable
Foreword	---
Definitions	---
Prescriber Instructions	---
Administrative Advice	---
Cautions	---

For more detail on PBAC's view, see section 7 "PBAC outcome".

4 Clinical place for the proposed therapy

4.1 The minor submission stated that other forms of mercaptopurine are solid dose forms and are not suitable for the paediatric patient group due to an inability to swallow a

solid tablet, less precise dose titration in patients under 9 years of age with the crushing of solid dose forms, and safety concerns to preparers when breaking up or crushing the cytotoxic tablet.

- 4.2 Therefore, the oral suspension would provide a more suitable dose form for young patients with ALL.

5 Comparator

- 5.1 The minor submission nominated mercaptopurine 50 mg tablets as the comparator.

6 Consideration of the evidence

Sponsor hearing

- 6.1 As a minor submission, there was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The minor submission cited the unpublished, comparative bioequivalence study of mercaptopurine suspension and tablets used to support the initial registration of the product with the TGA.

Comparative effectiveness

- 6.4 As the clinical evidence base presented in the minor submission cited a bioequivalence study, an assessment of comparative effectiveness in terms of patient relevant clinical health outcomes was not presented.

Comparative safety

- 6.5 The submission reported no deaths, serious adverse events or significant adverse events reported in the study. Three adverse events were recorded in three volunteers. One subject reported headache (mild intensity, considered unlikely to be drug-related). Two subjects had out-of-range blood test results post-study: one with elevated AST and one with leukopenia with neutropenia. Both were of moderate intensity and considered by the investigator to be possibly related to drug treatment. The overall evaluation of laboratory results showed no significant changes or trends between screening and final examination.

For more detail on PBAC's view, see section 7 "PBAC outcome".

Clinical claim

- 6.6 The submission claimed that the oral suspension and tablets have been shown to be bioequivalent for pharmacokinetic parameter of area under curve (AUC), and so can be expected to behave similarly in therapeutic use. The submission further noted that the liquid formulation is absorbed more rapidly than the tablet, but claimed that this is unlikely to be of any clinical significance. The submission claimed that the safety profiles of oral mercaptopurine oral suspension and mercaptopurine tablets do not differ in any way.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Economic analysis

- 6.7 A cost-analysis was presented in the submission as part of the estimates of the net financial implications to the government health budget.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Estimated PBS usage & financial implications

- 6.8 The submission’s estimates are summarised in the table below:

	Year 1	Year 2	Year 3	Year 4	Year 5
No. of patients treated with the oral suspension	█	█	█	█	█
Cost of oral suspension to PBS	█	█	█	█	█
Reduction in cost of tablets	█	█	█	█	█
Total net cost to the PBS	█	█	█	█	█

Source: Tables 5-6 and 5-8 of the Submission, p.39 and 41

The redacted table above shows the estimated patients treated to be less than 10,000 per year and the estimated financial implications to be less than \$10 million per year

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

7 PBAC outcome

- 7.1 The PBAC recommended listing mercaptopurine oral suspension as an unrestricted benefit on the basis of a clinical need existing for this particular dose form.
- 7.2 The PBAC considered that the level of clinical evidence presented in the minor submission to be reasonable in the context of a listing for which the likely volume and proportion of use is expected to be small. The PBAC noted that the submission’s main focus was to justify the clinical need for an oral dose form suitable for paediatric patients. The PBAC accepted the justification provided. The submission’s estimates of use and financial implications also appeared reasonable.

- 7.3 With respect to the submission’s proposed Authority Required (Streamlined) listing, the PBAC considered that mercaptopurine was unlikely to be used for indications outside of the TGA registered indication and so an unrestricted benefit listing, consistent with the tablets, was recommended.
- 7.4 The PBAC noted that the minor submission sought PBS listing of the mercaptopurine oral suspension 20 mg/mL at a higher price (DPMQ ██████ for 100 mL) than the tablet. The PBAC further noted that the cost of liquid formulations in general are typically higher (per mg), than solid dose formulations and held no objections to a final price of mercaptopurine oral suspension being set within the current range of general price differentials between liquid formulations and solid dose formulations.
- 7.5 The PBAC advised, under Section 101 (4AB) of the *National Health Act*, that the following circumstances exist in relation to the pharmaceutical item mercaptopurine oral suspension 20 mg per mL, 100 mL - oral:
- (a) It represents suitable therapy for paediatric patients with acute lymphoblastic leukaemia
 - (b) It is suitable for paediatric patients who are unable to swallow a solid dose formulation; and
 - (c) No other form of mercaptopurine is suitable for this subgroup because other formulations of mercaptopurine are solid dose forms.
- 7.6 The PBAC advised that mercaptopurine oral suspension is not suitable for prescribing by nurse practitioners.
- 7.7 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer
MERCAPTOPURINE				
mercaptopurine 20 mg/mL oral liquid, 100 mL	1	100 mL	2	Allmercap LM

Unrestricted benefit

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to

recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.