

## 6.10 RIFAMPICIN

### **Capsule 150 mg, Capsule 300 mg, Rimycin 150<sup>®</sup>, Rimycin 300<sup>®</sup>, Alphapharm Pty Ltd**

#### **1 Purpose of application**

- 1.1 The minor submission sought to extend the indication for rifampicin to include the treatment of *Mycobacterium ulcerans* infection (Buruli ulcer).

#### **2 Background**

- 2.1 The epidemic of Buruli ulcer in Australia is worsening, with a rapid increase in cases, new areas being affected, and an increase in the severity of the presentation. The disease results in high direct and indirect costs to patients: a single 100 capsule pack of rifampicin 300 mg on the private market retails for about \$250. The average patient requires 2 packs and also pays for diagnostics and other fees as part of their treatment.
- 2.2 Rifampicin is used in combination with other antibiotics for the treatment of Buruli ulcer, but is not TGA-registered or PBS-listed for this indication.

#### **Registration status**

- 2.3 Rimycin<sup>®</sup> was TGA registered on 10 March 1994, and is indicated for:
- tuberculosis,
  - leprosy (lepromatous leprosy and dimorphous leprosy),
  - lepromatous, dimorphous, indeterminate and tuberculoid leprosy resistant to sulfones and other anti-leprosy drugs,
  - as an alternative drug in all those patients having true drug allergy to the more commonly used anti-leprosy drugs,
  - prophylaxis of meningococcal disease in close contacts of known cases and in carriers (rifampicin is not indicated for the treatment of meningococcal infections), and
  - prophylaxis of household contacts of patients with *Haemophilus influenzae* type B.
- 2.4 Alphapharm has submitted an application to the TGA, and was granted Orphan Status and Priority Review Designation on 21 January 2020 for the addition of the following indication to the TGA registration for Rimycin 150 and Rimycin 300:
- For the treatment of *Mycobacterium ulcerans* infections (Buruli ulcer). Rifampicin is usually recommended to be used in combination with another antibiotic for the treatment of Buruli ulcer.

- 2.5 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, no TGA documents were available. The TGA evaluation report is expected in late July 2020.

### **Previous PBAC consideration**

- 2.6 Rifampicin for the treatment of Buruli ulcer has not been considered by the PBAC previously.
- 2.7 The Chief Medical Officer wrote to the PBAC in mid-2018 requesting consideration of a PBS listing for rifampicin for Buruli ulcer in response to the worsening outbreak in Victoria. At the request of the PBAC Executive, the Department then contacted the sponsor (Alphapharm) to encourage it to apply to the TGA and the PBAC to have the Buruli ulcer indication added to both the Australian Register of Therapeutic Goods and to the PBS listings for rifampicin.
- 2.8 Rifampicin capsules are currently PBS listed for the treatment of leprosy, meningococcal disease, and *Haemophilus influenzae* type B, as shown in Table 1.

**Table 1: Current PBS indications for rifampicin**

PBS item	Indication	Authority	Strength, qty	AEMP
1981G	Meningococcal disease <i>Haemophilus influenzae</i> type B	Restricted Benefit	150 mg capsule, 10	\$21.26
1982H	Leprosy	Authority Required	150 mg capsule, 100	\$21.26
1984K	Meningococcal disease <i>Haemophilus influenzae</i> type B	Restricted Benefit	300 mg capsule, 10	\$9.70
1983J	Leprosy	Authority Required	300 mg capsule, 100	\$9.70

Source: PBS website (sourced June 2020)

### **Population and Prevalence**

- 2.9 According to the World Health Organization (WHO), in 2018, 358 cases of Buruli ulcer were reported in Australia, the highest number of any country that reported data to the WHO. Of the 358 cases, 340 were from Victoria. There were 294 notified cases for Victoria in the 12 months to 20 September 2019.<sup>1</sup> The outbreak has worsened in recent years, with annual totals for 2016, 2017 and 2018 of 182, 277 and 340, respectively.
- 2.10 The national rate of infection for Buruli ulcer was 1.58 per 100,000 for the 12-month period 21 September 2018 to 20 September 2019<sup>2</sup>.

*For more detail on PBAC's view, see section 5 PBAC outcome.*

## **3 Requested listing**

- 3.1 The submission requested new listings of rifampicin 150 mg and 300 mg capsules to include the new indication with clinical criteria.

<sup>1</sup> [www.health.vic.gov.au/ideas/downloads/daily\\_reports/rptVS\\_SNIDSVictorianSummary\\_GR.pdf](http://www.health.vic.gov.au/ideas/downloads/daily_reports/rptVS_SNIDSVictorianSummary_GR.pdf)

<sup>2</sup> Calculated using ABS 2011 estimated resident population (total 22,620,600)

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer	
RIFAMPICIN rifampicin 150 mg capsule, 10	NEW	12	120	0	Rimycin 150®	Alphapharm Pty Ltd
rifampicin 300 mg capsule, 10	NEW	12	120	0	Rimycin 300®	Alphapharm Pty Ltd
rifampicin 150 mg capsule, 100	NEW	1	100	0	Rimycin 150®	Alphapharm Pty Ltd
rifampicin 300 mg capsule, 100	NEW	1	100	0	Rimycin 300®	Alphapharm Pty Ltd

**Restriction Summary NEW / Treatment of Concept: NEW**

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Type / Method:</b> <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required - Streamlined
<b>Indication:</b> Mycobacterium ulcerans infections (Buruli ulcer)
<b>Clinical criteria:</b> Treatment must be used in combination with another antibiotic for the treatment of Buruli ulcer.

## 4 Consideration of evidence

### *Sponsor hearing*

4.1 There was no hearing for this item as it was a minor submission.

### *Consumer comments*

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

### *Clinical evidence*

4.3 The minor submission presented a Clinical Review that was written by an infectious diseases physician. The report was completed on 29 October 2019 and provided to Alphapharm Pty Ltd to facilitate that sponsor's development of a submission to the TGA to extend the indication of rifampicin to include treatment of patients with Buruli ulcer.

4.4 The report concluded that the efficacy and safety profile of rifampicin for Buruli ulcer is favourable. The clinical reviewer recommended that the TGA indication of rifampicin should be extended to include Buruli ulcer and that the treatment be rifampicin 10 mg/kg/day to a maximum of 600 mg/day plus a second oral agent consisting of:

- clarithromycin 7.5 mg/kg twice a day – up to 500 mg per dose i.e. maximum of 1000 mg/day; or
- moxifloxacin 400 mg four times a day (adults only); or
- ciprofloxacin 500 mg twice a day (adults only).

- 4.5 Clarithromycin has Unrestricted PBS listings. Ciprofloxacin is listed on the PBS but is not able to be used for Buruli ulcer, and moxifloxacin is not PBS listed.
- 4.6 The clinical reviewer recommended the usual treatment duration of 8 weeks, but noted that longer courses may be needed for more complicated cases of Buruli ulcer, including those with related osteomyelitis.

**Drug cost/patient/course: \$262.92**

- 4.7 The above calculation assumed a maximum dose of 600 mg/day and a DPMQ of \$21.91 for 10 capsules of rifampicin 300 mg, for a course of 8 weeks i.e. a total of 112 capsules (for which 12 packs would be required). However, the actual cost may differ in practice due to weight-based dosing and other variations in individual patient needs. For example, for a child requiring a 450 mg/day dose, the child would require 6 packs each of the 150 mg and 300 mg 10 capsule packs, and the treatment would cost \$675.

**Estimated PBS usage & financial implications**

- 4.8 The minor submission requested that there be no change to the current pricing structure of the product. The AEMP of rifampicin 150 mg is \$21.26 and the AEMP for rifampicin 300 mg is \$9.70.
- 4.9 The minor submission did not provide any estimates of PBS usage or financial estimates or implications to the PBS outside of what was presented in the Clinical Review.
- 4.10 The Secretariat noted that it was difficult to estimate the number of patients based on PBS utilisation data as there are currently no PBS treatments for Buruli ulcer. Furthermore, the dosing for rifampicin in Buruli ulcer is weight based and the treatment duration can vary more depending on the severity of the condition.
- 4.11 The Secretariat has provided estimates of prescriptions over six years, as outlined in Table 2. The estimated net cost to the PBS is less than \$10 million over the first 6 years of listing.

**Table 2: Estimated PBS utilisation and financial estimates**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Buruli ulcer case rate (1.58 per 100,000) <sup>a</sup>	0.000016	0.000016	0.000016	0.000016	0.000016	0.000016
Australian population <sup>b</sup>	25,873,480	26,301,274	26,727,025	27,147,199	27,562,195	27,970,435
Incident patients <sup>c</sup>	409	416	422	429	435	442
Number of packs <sup>d</sup>	█	█	█	█	█	█
Cost at DPMQ (\$21.91) <sup>c</sup> / Net cost to PBS/RPBS (assuming no co-pay)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Co-pays (assuming full co-pay)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS/RPBS (assuming full co-pay)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Compiled by the DUSC Secretariat.

Note:

<sup>a</sup> Derived from the number WHO reported cases (n=358) relative to the estimated resident population (n=22,620,600).

<sup>b</sup> 3222.0 Population Projections, Australia. Table B9. Population projections, by age and sex, Australia - Series B.

<sup>c</sup> Calculated as incidence applied to total Australian population.

<sup>d</sup> Assume █ packs of rifampicin 300mg (10 pack) per patient

The redacted table shows that at Year 6, the estimated number of packs was less than 10,000 and the net cost to the PBS would be less than \$10 million.

- 4.12 Given that there are no PBS listed items specifically indicated for Buruli ulcer, it was difficult to estimate the different co-payment populations. The net cost to the PBS/RPBS was calculated for lower (assuming full co-payment) and upper (assuming no co-payment) bounds, resulting in a total over 6 years between less than \$10 million and less than \$10 million.

For more detail on PBAC’s view, see section 5 PBAC outcome.

## 5 PBAC Outcome

- 5.1 The PBAC deferred making a recommendation to change the listing of rifampicin on the PBS as the TGA Delegate’s Overview was not available at the time of consideration. However, the PBAC was of a mind to recommend the Authority Required (Telephone/Electronic/Emergency) listing of rifampicin for the treatment of *Mycobacterium ulcerans* infection (Buruli ulcer) if the TGA approves the new indication.
- 5.2 The PBAC noted that there is a worsening epidemic of Buruli ulcer in Australia and that rifampicin, one of the key treatments for Buruli ulcer, is not TGA-registered or PBS-listed for this indication.
- 5.3 The PBAC noted the clinical evidence provided and that the clinical reviewer had considered that the efficacy and safety profile of rifampicin for Buruli ulcer was favourable.
- 5.4 The PBAC noted that rifampicin is able to be prescribed by nurse practitioners.
- 5.5 The PBAC noted that the Early Supply Rule does not apply to other rifampicin listings and advised that the rule should not apply.
- 5.6 The PBAC advised that if recommended for listing, under Section 101(3BA) of the *National Health Act 1953*, rifampicin should not be treated as interchangeable with any other drugs on an individual basis.

### Outcome:

Deferred

## 6 Recommended listing

- 6.1 Add new PBS indication/listing:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
RIFAMPICIN rifampicin 150 mg capsule, 10	NEW	12	120	0	Rimycin 150®	Alphapharm Pty Ltd
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**Restriction Summary NEW / Treatment of Concept: NEW**

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
<b>Restriction Type / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
<b>Indication:</b> Mycobacterium ulcerans infections (Buruli ulcer)
<b>Clinical criteria:</b> Treatment must be used in combination with another antibiotic for the treatment of Buruli ulcer.

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **7 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **8 Sponsor's Comment**

The sponsor had no comment.

## Addendum to the July 2020 PBAC Minutes:

### 4.01 RIFAMPICIN

**Capsule 150 mg, Capsule 300 mg,  
Rimycin 150<sup>®</sup>, Rimycin 300<sup>®</sup>,  
Alphapharm Pty Ltd**

## 9 Background

- 9.1 At its July 2020 meeting, the PBAC deferred making a recommendation to extend the indication for rifampicin to include the treatment of *Mycobacterium ulcerans* infection (Buruli ulcer) until the TGA Delegate's Overview was available. However, the PBAC was of a mind to recommend the Authority Required (Telephone/Electronic/Emergency) listing of rifampicin for the treatment of *Mycobacterium ulcerans* infection (Buruli ulcer) if the TGA approves the new indication.
- 9.2 The TGA Delegate's Overview was provided on 2 September 2020.
- 9.3 The TGA Delegate's Overview stated that consideration by the Advisory Committee on Medicines (ACM) was not required and that the ARTG indication of rifampicin would be extended to include the treatment of *Mycobacterium ulcerans* infection (Buruli ulcer).
- 9.4 The TGA Delegate considered that the indication on the product information (PI) should state that "rifampicin must be used in combination with another anti-*Mycobacterium ulcerans* antibiotic."

## 10 PBAC Outcome

- 10.1 The PBAC recommended the Authority Required (Telephone/Electronic/Emergency) listing of rifampicin for the treatment of *Mycobacterium ulcerans* infection (Buruli ulcer).
- 10.2 The PBAC noted that the requested clinical criteria for the PBS listing was in line with the TGA Delegate's recommendation for the indication on the PI, that the "treatment must be used in combination with another antibiotic for the treatment of Buruli ulcer."

### Outcome:

Recommended

## 11 Recommended listing

- 11.1 Add new PBS indication/listing:

Public Summary Document – July 2020 PBAC Meeting

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## 12 Context for Decision

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## 13 Sponsor's Comment

The sponsor had no comment.