6.10 RIFAXIMIN
Tablet, 550mg,
Xifaxan®, Norgine Pty Limited

1 Purpose of Application

1.1 The minor submission requested a change to the existing listing for rifaximin from Authority Required to Authority Required (STREAMLINED).

2 Requested listing

2.1 The minor submission requested a change in the restriction level of the current listing from Authority Required to Authority Required (STREAMLINED). No other changes to the existing listing were requested.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RIFAXIMIN Tablet 550 mg, 56	1	5	Xifaxan	Norgine Pty Limited

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Prevention of hepatic encephalopathy
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Treatment criteria:	Must be treated by a gastroenterologist or hepatologist or in consultation with a gastroenterologist or hepatologist.
Clinical criteria:	The treatment must be in combination with lactulose, if lactulose is tolerated; AND Patient must have had prior episodes of hepatic encephalopathy.
Administrative advice:	**Note:** No increase in the maximum quantity or number of units may be authorised. **Note:** No increase in the maximum number of repeats may be authorised.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Background

Registration status

3.1 Rifaximin 550 mg tablet was TGA registered on 17 May 2012 for prevention of the recurrence of hepatic encephalopathy (HE) where other treatments have failed or are contraindicated (p5, TGA approved Xifaxan 550 mg Product Information (PI)).

3.2 Subsequently, rifaximin 200 mg tablet was TGA registered on 26 May 2015 for treatment of patients aged 12 years or more with travellers' diarrhoea caused by non-invasive strains of *Escherichia coli* (p5, TGA approved Xifaxan 200 mg PI). Rifaximin 200 mg is not currently listed on the PBS. The submission stated that rifaximin 200 mg tablets is available on the private market and is priced similarly to the PBS general co-payment.

For more detail on PBAC's view, see section 6 PBAC outcome.

Previous PBAC considerations

3.3 In November 2011 and July 2012, the PBAC rejected major (re)submissions for rifaximin for the prevention of HE based on uncertain and unacceptable cost effectiveness (Rifaximin Public Summary Documents (PSD), November 2011 and July 2012).

3.4 The PBAC recommended rifaximin in April 2013 for the prevention of HE, subsequent to its November 2012 deferral of a minor resubmission. In November 2012, the PBAC considered that the likely number of patients treated with rifaximin was uncertain, noting the potential for substantial leakage beyond the requested PBS population into treatment of irritable bowel syndrome (IBS) and travellers' diarrhoea. The PBAC therefore recommended that a Risk Sharing Arrangement (RSA) would be required to be negotiated in order to manage Government expenditure should PBS listing of rifaximin be achieved. The PBAC also noted expert advice expressing concerns about the potential for the development of antimicrobial resistance (AMR). (rifaximin PSD, April 2013)[1]

3.5 In November 2016, the PBAC noted a DUSC report on predicted versus actual use of rifaximin for HE. The DUSC report stated that in the period from 1 December 2013 to 31 March 2016, 2,892 people were supplied at least one PBS/RPBS prescription for rifaximin. The number of patients supplied rifaximin was higher than predicted in both the first and second years of listing. The number of prescriptions per patient per year was lower than estimated. The report noted that this may indicate poor adherence or intermittent use. (PBAC outcomes, Consideration of the DUSC report, November 2016)[2]

3.6 The PBAC considered that the following additional extracts from the DUSC report (Rifaximin: 24 month predicted versus actual analysis, DUSC Public Release Document (PRD), September 2016)[3] were relevant to the current minor submission:

- "DUSC also discussed whether off-label use or use outside the restriction could be contributing to higher patient numbers than estimated, but considered the Authority Required restriction should help mitigate against this."

[1] URL: http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2013-04/rifaximin
[2] URL: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2016-11/dusc-report-2016-11.pdf
[3] URL: http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2016-09/rifaximin-24-month-review-2016-09

- "DUSC recalled from its consideration of the rifaximin submission (October 2011 meeting) that it had thought people would have fewer prescriptions per year than estimated by the submission. There was considerable uncertainty as to whether rifaximin would be prescribed intermittently or continuously and for how long. Despite being indicated for prevention of HE, DUSC recalled that it had considered it would be conceivable that patients may only take rifaximin when experiencing exacerbations of HE. DUSC added that other reasons for the lower than predicted prescription numbers might be poor treatment persistence or adherence. DUSC also noted that there might be supervening clinical events that remove the need for rifaximin, such as receiving a liver transplant or death."
- "The sponsor stated that a contributing factor towards a drop in follow-up/repeat prescribing might be the paperwork that a prescriber must complete in order to prescribe rifaximin on the PBS. The sponsor requested that rifaximin be considered for a STREAMLINED authority listing. DUSC noted that rifaximin is a phone authority therefore a prescriber would not be required to complete large amounts of paperwork to meet PBS criteria. Further, at the August 2015 Post-Market Review of Authority Required PBS listings meeting, the PBAC recommended that rifaximin remain Authority Required."
- "…the risk of resistance from rifaximin use is real but difficult to quantify. As antimicrobial resistance is complex and multifactorial, DUSC considered it is difficult to determine the contribution of individual factors, such as rifaximin prescribing. Additionally, antimicrobial resistance takes a number of years to become apparent and rifaximin has only been PBS-listed for a short period of time."

For more detail on PBAC' view, see section 6 PBAC outcome.

4 Population and disease

4.1 Hepatic encephalopathy (HE) is a reversible neuropsychiatric disorder that arises due to the impaired liver function resulting in high levels of circulating toxins, particularly ammonia, affecting the brain.

4.2 Current management strategies include the identification of precipitating factors and the initiation of pharmacologic therapies aimed at modulating intestinal flora and reducing levels of ammonia and other gut-derived toxins. Lactulose and rifaximin are two commonly used treatments for the management of HE.[4]

For more detail on PBAC' view, see section 6 PBAC outcome.

[4] Waghray A1, Waghray N, Kanna S, Mullen K. Optimal treatment of hepatic encephalopathy. Minerva Gastroenterol Dietol. 2014 Mar;60(1):55-70.

5 Consideration of the evidence

Sponsor hearing

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

Consumer comments

5.2 The PBAC noted and welcomed the input from one health care professional via the Consumer Comments facility on the PBS website. The comment stated that a STREAMLINED Authority listing would make it easier for prescribers to appropriately prescribe rifaximin for patients with HE.

Current situation

5.3 The minor submission claimed that the current Authority level impedes access to rifaximin for patients with liver disease and prior episodes of HE, and therefore requested a change to a STREAMLINED Authority to facilitate access and improve health outcomes for these patients and to reduce the time burden on prescribers (p8 of the submission).

5.4 To support this hypothesis, the submission presented a survey of 39 specialists (gastroenterologists/hepatologists) in Australia. The submission claimed that the results revealed :

- The time taken to obtain an authority approval code can be up to 10 minutes (mean = 5.5 minutes, median = 5 minutes).
- 18% of specialists felt that the need to obtain an authority code prevented them from prescribing rifaximin to eligible patients (with prior episodes of HE) to a moderate or large extent.
- 41% of specialists were aware of patients who ceased rifaximin because their GP did not apply for a new Authority script.
- 77% of specialists felt that, to a moderate or large extent, a STREAMLINED Authority listing for rifaximin would help them to more effectively treat and manage their patients for the prevention of recurrent HE.
- On average, a 3% increase is anticipated in the number of patients to whom they would prescribe rifaximin for the prevention of the recurrence of HE (with a revised upper mean estimate of 8%).

5.5 To address previous PBAC concerns regarding leakage and development of AMR (see paragraph 3.4), the submission presented an analysis of a 10% PBS sample dataset for the period December 2013 (first month of PBS listing) to September 2018 inclusive. As a minor submission, the analysis was not independently evaluated. The submission claimed that the analysis indicated:

- The number of patients initiating rifaximin each year under the current Authority Required listing was relatively stable, consistent with use only in new patients with HE (p19).
- No evidence was found to suggest that rifaximin was used outside its restriction into travellers' diarrhoea, irritable bowel syndrome and Crohn's disease (p14).
- A significant portion of rifaximin use was episodic, with treatment period averaging between 75 and 90 days, rather than continuous treatment as per recommendations, suggesting patients may use rifaximin during exacerbations of liver disease (p20).
- More than half of all prescriptions (initial or subsequent) were written by a GP (p18).

5.6 The submission suggested that the episodic nature of treatment may reflect issues in accessing rifaximin under the current Authority restriction. As noted in the survey (paragraph 5.4), 18% of specialists felt the current Authority restriction prevented them from prescribing rifaximin for eligible patients to a moderate or large extent.

5.7 The submission also presented an updated literature review since the November 2011 and July 2012 PBAC (re)submissions. The submission and the pre-PBAC response stated that the review showed little evidence to support the risk of developing AMR with rifaximin. As a minor submission, the literature review was not independently evaluated.

5.8 The submission and pre-PBAC response noted that no changes to the risk management plan or other risk minimisation activities were required during the reporting period (30 May 2017 to 29 May 2018) in the most recent Periodic Safety Update Report (PSUR) for rifaximin. Additionally, only 6 cases of AMR had been reported over the 38-year cumulative period from April 1985 to May 2018.

Estimated PBS usage & financial implications

5.9 The minor submission estimated a net cost to the PBS/RPBS of less than $10 million at Year 6, with a total net cost to the PBS/RPBS of less than $10 million over the first six years, following the proposed change to a STREAMLINED Authority. This is summarised in Table 1 below as well as the expected patient/packs numbers

5.10 The submission made the following assumptions regarding utilisation under the current listing:

- Annual growth in the number of packs dispensed would continue to reduce by 2.5% each year, in line with the reduction in annual growth between 2017 and 2018.
- The number of patients was estimated from the number of packs dispensed divided by the average number of packs per patient per year ([redacted] packs per patient per year) in 2017 based on the PBS 10% sample data.

- The cost to PBS/RPBS was calculated using the April 2019 published DPMQ ($466.72) and the average co-payment per pack ($11.62) which was derived based on the distribution of rifaximin across patient beneficiary categories in 2018.

5.11 The submission assumed that the change to a STREAMLINED Authority would result in an increase in the number of packs dispensed under the current listing by 1.5% in Year 1, and 3% in Year 2 and thereafter. This assumption was based on the weighted mean increase in patient numbers projected in the survey of 39 specialists.

Table 1: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	2019	2020	2021	2022	2023	2024
Estimated extent of use under the current Authority Required listing						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of packs dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated additional extent of use under the proposed Authority Required (STREAMLINED) listing						
Number of additional patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of additional packs dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications under the proposed Authority Required (STREAMLINED) listing						
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for the current Authority Required listing						
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 5.5, p33, Table 5.6, p34 and Table 5.7, p36 of the submission

5.12 The minor submission stated that the increase in patient numbers because of the proposed change was uncertain. The submission presented a sensitivity analysis in which a higher increase in patient numbers (of 8%) was applied. In this scenario, the net cost to the PBS/RPBS in Year 6 following the proposed change would be around less than $10 million. However, the submission also noted that the median increase in patient numbers from the survey was 0% in this scenario, there would be nil additional cost to the PBS/RPBS.

5.13 As a minor submission, the financial estimates have not been independently evaluated.

Financial Management – Risk Sharing Arrangements

For more detail on PBAC' view, see section 6 PBAC outcome.

5.14 Rifaximin is listed on the PBS in conjunction with a Risk Sharing Arrangement that includes a two-tier subsidisation cap. Where Subsidisation Cap (SC) 1 is breached, it

results in 30% of Commonwealth expenditure above SC1 being reimbursed by the sponsor. Where SC2 is breached, it results in 60% of Commonwealth expenditure above SC2 being reimbursed. The term of the current Deed ended on 30 November 2018 and will continue to operate under the terms of the last year of the Deed until the Deed is by mutual agreement, either terminated or a new Deed negotiated. SC1 was breached in Years 2 to 5 of the current Deed. The minor submission did not include the impact of the current RSA on the effective net cost to the PBS/RPBS.

6 PBAC Outcome

6.1 The PBAC did not recommend the requested change to the PBS listing of rifaximin to lower the authority level from Authority Required to Authority Required (STREAMLINED) for prevention of recurrent HE.

6.2 The PBAC recalled that it previously noted the potential for substantial leakage beyond the treatment of patients with recurrent HE into treatment of IBS and travellers' diarrhoea (see paragraph 3.4). The PBAC also recalled expert advice expressing concerns about the potential for the development of AMR. The PBAC noted the 10% PBS sample dataset presented in the submission, and agreed with the submission that leakage of rifaximin was not evident in this data; however, the PBAC noted the data represents prescribing under the current authority level and considered that the data demonstrated the effectiveness of the current authority level. The PBAC advised the current authority should remain unchanged to assist in managing the risks of leakage and the potential for the development of AMR.

6.3 The PBAC noted the survey of 39 Australian specialists (gastroenterologists/ hepatologists) included in the submission, which indicated the median time taken to obtain an Authority approval number by telephone was 5 minutes. The PBAC noted that the survey did not include GPs, while over half of prescriptions for initial and continuing treatment were written by a GP. The PBAC did not consider the current requirement for a telephone authority to be administratively burdensome. The PBAC considered it was unlikely that the requirement for a telephone authority would prevent clinically appropriate prescribing of rifaximin to eligible patients.

6.4 The PBAC noted that this submission is not eligible for an Independent Review as it is not for an entirely different disease or an objectively different subtype of the same disease or the same condition but where treatment is targeting a different population or a different stage of disease.

Outcome:

Rejected

7 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.

8 Sponsor's Comment

The sponsor had no comment.