PUBLIC SUMMARY DOCUMENT
Product: Rifaximin, tablet, 550 mg, Xifaxan®
Sponsor: Norgine Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

Re-submission for a Restricted Benefit listing, in combination with lactulose, for the prevention of hepatic encephalopathy (HE) in adult patients who have had prior episodes of hepatic encephalopathy.

2. Background

Rifaximin was considered by the PBAC at the November 2011 meeting and rejected on the basis of high and very uncertain cost-effectiveness.

3. Registration Status

Rifaximin was registered by the TGA on 17 May 2012 for the following indication:

- Prevention of the recurrence of hepatic encephalopathy where other treatments have failed or are contraindicated.

4. Listing Requested and PBAC's View

Restricted Benefit **OR**
Authority Required (STREAMLINED)
Prevention of hepatic encephalopathy in an adult patient who has had prior episodes of hepatic encephalopathy. Treatment is to be in combination with lactulose where lactulose therapy can be tolerated.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Hepatic Encepatholopathy (HE) is a reversible neuropsychiatric disorder that arises due to hepatic insufficiency. In the late stages of chronic liver failure and fulminant hepatic failure the body is unable to eliminate toxins, particularly ammonia, impairing brain function . Early symptoms include changes in sleep patterns, apathy, irritability and confusion. Severe symptoms include delirium and coma can occur.

Most treatments for HE, such as lactulose, are aimed at reducing the production of ammonia in the gut. This reduces the amount the liver needs to eliminate, there is then less ammonia in the bloodstream reducing the neurotoxic effects on the brain and thus the symptoms of HE.

More information about HE can be found on the following link:
http://www.liverfoundation.org/abouttheliver/info/hepaticencephalopathy/ and here
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001347/

The submission proposed that the place in therapy of rifaximin was as an add-on to other currently available treatments, including lactulose, for the prevention of episodes of HE.

6. Comparator

The submission nominated lactulose alone (with placebo) as the comparator. The PBAC previously agreed that placebo as add-on therapy to lactulose is the appropriate comparator in the context of concomitant treatment of rifaximin with lactulose.

7. Clinical Trials

The basis of the re-submission was trial RFHE3001, which was considered by PBAC in November 2011. It was a randomised, double-blind trial with 140 and 159 patients randomised to rifaximin (± lactulose) and placebo (± lactulose), respectively. Lactulose use in the trial was optional for subjects if they were already taking lactulose at baseline – the majority (~91%) of patients in the trial were taking lactulose. Patients in the trial were followed for 6 months or until they experienced a breakthrough episode of overt HE, at which point they were censored. Patients were enrolled if they had experienced at least two episodes of HE (Conn score of ≥2) associated with cirrhosis or portal hypertension during 6 months prior to screening and a score of 25 or less on the Model for End-Stage Liver Disease (MELD) scale.

The table below details the published trial RFHE3001 and associated reports presented in the submission:

Trials and associated reports presented in the submission

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
RFHE3001	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerability of Rifaximin 550 mg BID for 6 Months in Preventing Hepatic Encephalopathy.	13 April 2009 RFHE3001 Clinical Study Report
Bass, N. M et al	Rifaximin treatment in hepatic encephalopathy.	2010 New England Journal of Medicine 362(12): 1071-1081.
Neff, G. et al	Rifaximin reduces the risk of hospitalizations in patients with previous episodes of hepatic encephalopathy: Results from a phase 3 placebo-controlled trial.	2009 Gastroenterology 136(5): A11-A12.
Sanyal, A. et al	Rifaximin treatment improved quality of life in patients with hepatic encephalopathy: Results of a large, randomized, placebo-controlled trial.	2010 Journal of Hepatology 52: S7.
Sanyal, A. et al	Rifaximin decreases venous ammonia concentrations and time-weighted average ammonia concentrations correlate with overt hepatic encephalopathy (HE) as assessed by Conn score in a 6-month study.	2010 Journal of Hepatology 52: S84.
Sanyal, A. et al	Chronic administration of rifaximin for the maintenance of remission of hepatic encephalopathy: A subgroup analysis of a phase 3 trial.	2009 Journal of Hepatology 50: S90.
Bass, N. et al	Rifaximin is effective in maintaining remission in hepatic encephalopathy: Results of a large, randomized, placebo-controlled trial.	2009 Journal of Hepatology 50: S39.
Brown, R. S. et al	Rifaximin significantly improved Critical Flicker Frequency, and time-weighted CFF correlated with overt hepatic encephalopathy as assessed by Conn score in a 6 month study.	2009 Hepatology 50: 449A-450A.
Mullen, K. et al	Safety of rifaximin in patients with hepatic encephalopathy: Results of a randomized, phase 3,	2009 Journal of Hepatology 50: S84-

	placebo-controlled clinical trial.	S85.
Poordad, F. et al	The protective effect of rifaximin (1100 mg daily) from hepatic encephalopathy observed in a double-blind placebo controlled study is substantiated and durable over the long term.	2009 Hepatology 50: 448A-449A.
Sigal, S. Et al	The effect of prognostic factors on the maintenance of remission in hepatic encephalopathy patients treated with rifaximin.	2009 Gastroenterology 136(5): A27-A28.

8. Results of Trials

The primary outcome of Trial RFHE3001 was the time to first breakthrough overt HE episode. This was defined as either an increase in the Conn score to grade ≥2; or for patients who entered the trial with a Conn score of zero, it was defined as an at least one grade increase in both the Conn and asterixis scores from baseline. Trial RFHE3001 only reported the time to first HE event over 6 months and not any subsequent events in these patients.

Results of the primary outcome are presented in the table below:

First breakthrough episodes of overt HE in Trial RFHE3001

Trial RFHE3001	**Rifaximin n/N (%)**	**Placebo n/N (%)**	**HR (95% CI) p-value**
Primary analysis[a]	31/140 (22.1%)	73/159 (45.9%)	**0.421 (0.276 – 0.641) p<0.0001**
Sensitivity analysis[b]	34/140 (24.3%)	73/159 (45.9%)	**0.461 (0.307, 0.693) p=0.0001**

Abbreviations: CI = Confidence interval, HR=hazard ratio

[a] the results for those patients who terminated the trial early for reasons other than overt HE are not included

[b] including the results of patients who terminated the trial early for reasons other than overt HE

Text in bold indicate statistically significant differences at 5% level

The results of additional analyses for the proportion of patients having a breakthrough episode of overt HE in Trial RFHE3001 are shown in the table below:

Number of patients with first breakthrough episodes of overt HE in Trial RFHE3001

Analysis	**Rifaximin n/N (%)**	**Placebo n/N (%)**	**RD (95% CI)**	**NNT (95% CI)**	**RR (95% CI)**	**OR (95% CI)**
Primary	31/140 (22.1%)	73/159 (45.9%)	**-0.24 (-0.34, -0.13)**	**4 (3, 8)**	**0.48 (0.34, 0.68)**	**0.34 (0.19, 0.57)**
Sensitivity	34/140 (24.3%)	73/159 (45.9%)	**-0.22 (-0.32, -0.11)**	**5 (3, 9)**	**0.53 (0.38, 0.74)**	**0.38 (0.22, 0.64)**

Abbreviations: CI = Confidence interval, RD=risk difference, NNT=number needed to treat, RR=relative risk, OR=odds ratio

Text in bold indicate statistically significant differences at 5% level

Statistically significantly fewer patients treated with rifamixin experienced a first breakthrough episode of overt HE over the 6 month duration of the trial. The PBAC noted that as the trial reported first breakthrough events only the total number of HE events in the groups were not established and it is not known whether recurrent HE events are avoided. .

Another outcome of patient relevance was time to first HE-related hospitalisation, summarised in the table below:

Number of patients with at least one HE-related hospitalisation in Trial RFHE3001

Rifaximin n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT* (95% CI)	RR (95% CI)	OR (95% CI)
Proportion requiring hospitalisation					
19/140 (13.6%)	36/159 (22.6%)	**-0.091 (-0.177, -0.004)**	**11 (6, 250)**	**0.599 (0.361,0.995)**	**0.54 (0.29, 0.99)**
Proportion of HE events requiring hospitalisation*					
19/31 (61.3%)	36/73 (49.3%)	0.12 (-0.09, 0.31)	N/A	1.24 (0.84, 1.76)	1.63 (0.64, 4.23)

Text in bold indicate statistically significant differences at the 5% level

* not presented in the previous Commentary, but included for completeness

Statistically significantly fewer patients treated with rifaximin had HE-related hospitalisations when considered as a proportion of all patients. For patients experiencing a HE event, there was no difference in the proportion requiring hospitalisation between treatment groups.

No new adverse event data were presented in the re-submission.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed that rifaximin was superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.

The PBAC previously considered there was reasonable clinical evidence provided in Trial RFHE3001 to demonstrate that rifaximin in combination with lactulose reduces symptoms and hospitalisations in patients during episodes of HE, but there was uncertainty associated with the magnitude of the effect and in addition:

- There was no evidence to support the assumptions regarding reduced subsequent events the trial only reported the time to, and proportion of, patients having a first episode of overt HE.
- There was no evidence to support the assumptions regarding reduced duration of events and this was not reported in the trial.
- The additional benefit of combination therapy with lactulose may not be fully realised in clinical practice as optimal lactulose therapy may not be continued whilst on therapy with rifamixin. The PBAC noted that the results of rifamixin use were not clearly presented for the 9% of patients in the trial who were not taking lactulose;
- It was unclear whether rifaximin would be effective or safe in patients with a MELD score >25 as these patients were excluded from Trial RFHE3001.

The PBAC noted expert advice expressing concerns about the potential for the development of rifampicin resistant staphylococci.

10. Economic Analysis

The re-submission presented a cost-utility analysis based on superiority claims over placebo.

Compared to the November 2011 submission, the model structure was not changed substantially, with the exception that hospitalisations were now modelled as a proportion of HE events rather than independently and the time horizon of the "scenario analysis" was reduced from 5 to 2 years. Further changes were the assumption of 100% compliance (84.3%

in the previous submission) and the application of an additional disutility associated with HE-related hospitalisation.

The PBAC agreed the time frame was appropriate considering the prognosis of the disease. The PBAC noted that compliance was only estimated at 100% for the first 6 months, but that beyond that the extrapolation reduced compliance but maintained efficacy. The pivotal evidence for the assumptions was two retrospective studies involving 24 patients.

The incremental cost of rifaximin + lactulose versus lactulose alone was estimated to be between $15,000 - $45,000 per additional QALY gained at 6 months.

As the base case ICER was reported after only 6 months in the modelled economic evaluation and did not extend beyond the duration of the main trial (Trial RFHE3001) it was considered uncertain whether it was a true representation of the long term costs and benefits associated with rifaximin on the PBS.

The ICER was highly sensitive to the efficacy of rifaximin compared to placebo in preventing HE events, the assumption of differences in hospitalisation rates between the rifaximin and placebo groups (i.e. difference in ratio and duration) and the cost of hospitalisation in the placebo group.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the re-submission to be less than 10,000 over the first 5 years, at an estimated net cost to the PBS of between $30 - $60 million over the first 5 years .

12. Recommendation and Reasons

The PBAC recognised that there is a clinical need for a treatment that reduces the symptoms of hepatic encephalopathy (HE) and conssequent hospitalisations. The clinical advice presented at the hearing confirmed that rifaximin would be a useful adjunct to current medication for all patients with HE, particularly as current diagnostic techniques are limited and patients are generally only seen once symptoms become troublesome.

The PBAC recalled that in November 2011, it had agreed that the appropriate comparator was placebo as add-on therapy to lactulose in the context of concomitant treatment of rifaximin with lactulose.

The resubmission presented a single arm extension study of Trial RFHE3001, which was the pivotal trial in the November 2011 submission. As previously, the PBAC noted that the patient population in Trial RFHE3001 is narrower than the requested PBS population as it precludes patients with HE due to causes other than cirrhosis or portal hypertension, and patients with a model for end-stage liver disease (MELD) score greater than 25, who will be eligible for treatment with rifaximin under the proposed PBS restriction. The PBAC further noted that no data was presented for patients who are intolerant to lactulose.

The PBAC recalled that it had previously accepted there was some clinical evidence to demonstrate that rifaximin in combination with lactulose may reduce the frequency of symptoms and hospitalisations in patients with HE over 6 months, which was the trial

duration. However the efficacy of rifaximin is uncertain beyond 6 months of treatment. The PBAC reiterated that the magnitude of the treatment effect was uncertain and further considered that the estimate from the NEJM trial (Bass et. al.) may be an overestimate of the effect of rifaximin in clinical practice.

In regard to safety, the PBAC expressed concern about the potential for developing resistance to Staphylococci due to rifaximin use, and the lack of surveillance programs to monitor any changes. The PBAC noted clinical advice regarding the potential consequential risk of developing resistance to rifampicin from long term, constant use of rifaximin, even though the overall patient numbers receiving treatment with rifaximin may be relatively small. The PBAC also noted the clinical advice that episodic use was not clinically beneficial.

The resubmission presented an updated modelled economic evaluation. The PBAC considered that the structure of the model was reasonable, however noted that the inputs for duration of hospital stay and rate of hospitalisation were not based on the randomised trial data (NEJM). The PBAC considered that a difference in the length of hospital stay for the placebo arm compared to the rifaximin arm was likely but that the difference may be less than that used in the model (8 days for placebo versus 3 days for rifaximin). The PBAC noted that this difference is a significant driver of the cost effectiveness. The model uses 8 days for the lactulose alone arm from the Leevey et al study but the PBAC noted that the lactulose alone arm in this study had very low compliance. The Leevey study quoted an analysis of hospital discharges reporting an average hospital stay of 5.7 days in 40,012 patients with a primary diagnosis of hepatic encephalopathy.

Overall the PBAC considered that the rate of hospitalisation is less in patients treated with rifaximin, as reported in the pivotal study. However the multiplication factor of 2.1 that is used to estimate total hospitalisations in the model was not well justified and is not consistent with the NNT for hospitalisation reported by the pivotal study.

Therefore, the PBAC rejected the submission for rifaximin on the basis of high, uncertain, and unacceptable cost effectiveness.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

13. 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.

14. Sponsor's Comment

The sponsor has no comments.