PUBLIC SUMMARY DOCUMENT
Product: Rifaximin, tablet (film-coated), 550 mg, Xifaxan®
Sponsor: Norgine Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To request a Restricted Benefit listing for the prevention of a further recurrence or relapse in a patient who has already had an episode of hepatic encephalopathy (HE).

2. Background

This drug had not been previously considered by the PBAC.

3. Registration Status

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

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

4. Listing Requested and PBAC's View

Revised restriction suggested in the sponsor's Pre-Sub-Committee response:

Restricted Benefit
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 encephalopathy (HE) is a reversible neuropsychiatric disorder that arises due to hepatic insufficiency and results in the body being unable to eliminate toxins, particularly ammonia, from the blood stream. It occurs due to acute fulminant hepatic failure, and more often, in patients with chronic liver disease. HE can be classified into 3 subtypes- episodic (most common form), persistent and minimal. Early symptoms include reversal or changes in sleep pattern, apathy, irritability and personal neglect. In later stages, delirium and coma can arise with neurologic signs including hyperflexia, rigidity, myoclonus and severe hand tremor. As episodes of HE increase in severity and become clinical (overt) there is a deterioration in cognition functioning.

Most treatments for HE, such as lactulose, are aimed at reducing the production of ammonia in the gut, which reduces the amount in the bloodstream, which inturn reduces the neurotoxic effects on the brain and thus the symptoms of HE.

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

6. Comparator

The submission nominated lactulose alone (or placebo) as the comparator, which was considered appropriate by the PBAC in the context of concomitant treatment of rifaximin with lactulose.

7. Clinical Trials

The submission presented one randomised trial (Trial RFHE3001) that compared rifaximin 550 mg twice daily with placebo in patients with a history of at least two episodes of overt HE associated with cirrhosis or portal hypertension. 91% of patients in both arms of the trial had also received concomitant lactulose therapy.

For PBAC's view, see Recommendation and Reasons.

The following trial had been published at the time of submission:

Trials and associated reports presented in the submission

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
RFHE3001 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, placebo-controlled clinical trial.	2009 Journal of Hepatology 50: S84-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

In the primary efficacy analysis for Trial RFHE3001, statistically significantly fewer patients randomised to rifaximin treatment experienced breakthrough episodes of overt HE compared

to placebo over the 6 months of the trial, 31/140 (22.1%) and 73/159 (45.9%) of patients treated with rifaximin and placebo, respectively, experienced at least one breakthrough episode of overt HE during the trial follow up, HR (95%CI): 0.421 (0.276 – 0.641), p<0.0001.

In a sensitivity analysis of the trial outcomes to include the results for those patients who terminated the trial early for reasons other than overt HE, 34/140 (24.3%) and 73/159 (45.9%) patients from the rifaximin and placebo groups experienced at least one breakthrough episode of overt HE, HR(95%CI): 0.461 (0.307, 0.693), p=0.0001. The Conn score, a classification system to measure neurological symptoms in hepatic encephalopathy, was the main criteria used to determine the re-occurrence of HE in the trial. Conn scores range from 0 to 4 with a higher score indicating more severe impairment.

For the secondary endpoint, time to first HE related hospitalisation, the trial indicated that statistically significantly fewer patients experienced at least one hospitalisation for an occurrence of HE during treatment with rifaximin 13.6% compared to placebo 22.6%, RD (95%CI): -0.091 (-0/177, -0/003).

The overall incidence of adverse events (AEs), serious AEs, treatment related adverse reactions (ARs), withdrawal due to AEs and death were similar between the rifaximin and placebo treatment groups in Trial RFHE3001. Deaths were predominantly due to underlying liver disease. The incidence of individual AEs and SAEs were generally similar between the two treatment groups, except the incidence of anaemia (2.9% versus 0%, RD (95% CI): 0.02 (0.00, 0.06)) and the incidence of vomiting was higher in patients treated with rifaximin compared to placebo (2.1% versus 0%, RD (95%CI): 0.02 (0.00, 0.05)). There were also significantly more patients with treatment emergent AEs in the eye disorders class for the rifaximin group compared to placebo (13/140(9.3%) versus 3/159 (1.9%), RD (95%CI): 0.07 (0.02, 0.13)).

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. Overall, the periodic safety update report (PSUR) concluded that the benefit risk assessment for rifaximin remains unchanged and is adequately reflected in the company's reference safety information for rifaximin.

For PBAC's view on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described rifaximin as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.

The PBAC considered this is only reasonable in the context of concomitant treatment with lactulose rather than rifaximin as monotherapy, *see Recommendation and Reasons*.

10. Economic Analysis

A stepped economic evaluation was presented. The submission used cohort expected value analysis to estimate the incremental cost per additional QALY gained of rifaximin+lactulose versus lactulose treatment alone in the model.

The base case of the economic evaluation was restricted to the within trial period only. A subsequent scenario analysis was included to assess the potential longer term effects of treatments. This was based on an exponential extrapolation of the 6 month results from Trial RFHE3001 for the rifaximin+lactulose and placebo+lactulose treatment groups, for the proportion of patients without any breakthrough overt HE and the proportion of hospitalisations for HE for each monthly cycle over 5 years.

Survival was assumed to be the same for rifaximin+lactulose and lactulose treated patients.

The base case of the submission assumed that the duration of an episode of HE is the same as the duration of a hospitalisation for HE, that all patients are fully compliant (varied in a sensitivity analysis) with the medications and do not discontinue treatment prematurely and that there were no differences in adverse events or survival between the two treatment arms.

The utility values used in the model in the base case were derived from Wong et al (1998) and were used to estimate the QALY gained over the model duration from HE events avoided.

The final outcome used in the trial-based economic evaluation was the cost per additional QALY gained. Health outcomes used in the trial-based economic evaluation were the cost per additional patient in which HE avoided and cost per hospitalisation avoided.

Within the longer term scenario analysis, the occurrence of hospitalisations in the latter years was higher than occurrence of HE. The PBAC considered this was implausible as the model costs each of these hospitalisations as if they were the result of HE, but the number of hospitalisations is greater than the number of HE events. Cumulatively, over the entire longer term scenario analysis, the proportion of patients with an HE event was higher than the proportion hospitalised for such an event.

The incremental cost of rifaximin + lactulose versus lactulose alone was estimated to be between $45,000 - $75,000 per additional QALY gained at 6 months. As indicated bye the sponsor, the ICER was very sensitive to any small changes in the assumed costs or QALYs over this period.

The submission did not formally present the results of the economic evaluation extrapolated over 60 months.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The financial cost to the PBS was estimated by the submission to be between $10 - $30 million in Year 5 of listing. This was considered uncertain.

12. Recommendation and Reasons

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

The PBAC noted that the revised restriction proposed by the sponsor in its Pre-Sub-Committee response was consistent with the patient population from trial RFHE3001, of which 91% received concurrent treatment with lactulose and who had a history of at least 2 prior episodes of HE cirrhosis or portal hypertension. The PBAC noted that the current draft PI does not specify combination treatment of rifaximin with lactulose, although rifaximin is still undergoing evaluation by the TGA.

The PBAC expressed concern that the utilisation of rifaximin could be much greater than estimated as there is significant potential for rifaximin to be used in a much wider population at risk of HE or other indications such as travellers diarrhoea, various GI infections and irritable bowel syndrome, particularly if listed on the PBS as a Restricted Benefit. Therefore, the Committee considered that an Authority Required listing may be more appropriate to limit use beyond the restriction for prevention of further recurrence or relapse of HE.

The PBAC considered there was reasonable clinical evidence provided in trial RFHE3001 to demonstrate that rifaximin in combination with lactulose may reduce the frequency of symptoms and hospitalisations in patients due to episodes of HE, however there is uncertainty about the magnitude of the effect. The evidence provided suggests that there is no treatment effect between episodes and the natural history of the underlying disease remains unchanged. Therefore, the QoL difference is likely to be overall relatively small. The PBAC noted that the additional benefit of combination therapy may not be realised in clinical practice as patients may not continue with optimal lactulose therapy while on treatment with rifaximin. There is additional uncertainty about whether rifaximin will be used intermittently when patients experience an exacerbation of HE or continuously for the long term.

The PBAC also noted that the treatment effect of rifaximin in trial RFHE3001 appears to be greater than would be expected given evidence reported in other trials, which were excluded from the submission, measuring the efficacy of rifaximin in preventing HE.

The RFHE3001 trial population was not considered by the PBAC to be fully representative of those patients likely to access rifaximin on the PBS, as patients with more severe liver disease, ie those with a MELD score >25, who are at greater risk of HE were excluded and no clinical evidence was presented in patients intolerant to lactulose. The PBAC also noted that Conn scores at the lower end of severity (0-2) are difficult to categorise objectively and a one point change may be of uncertain clinical significance.

The PBAC considered that there is potential for development of antibiotic resistance with use of rifaximin, particularly in the context of long term chronic use as it may affect the durability of the individual response, the sustainability of efficacy and potential effects on antimicrobial resistance in the community. Despite seeking further advice from the National Health and Medical Research Council this issue remains unresolved.

The PBAC noted the following concerning issues in relation to the economic modelling:

- the model appears to consider HE events and hospitalisation as independent events rather than the usual practice of modelling hospitalisations as a constant proportion of an HE event;
- beyond 6 months, the proportion of HE events that are hospitalised increases rapidly (most rapidly in the placebo arm) which results in a situation where there are more hospitalisations due to HE than there are HE events;

- the model appears biased in favour of rifaximin, as the effect of the diverging hospital events is greatest in placebo patients;
- the model estimates a base case ICER between $45,000 - $75,000 per additional QALY gained at 6 months, there is major uncertainty associated with extrapolating this result to estimate the long term costs and consequences of rifaximin treatment beyond those observed in Trial RFHE3001;
- the model assumes that the length of hospitalisations is a proxy for the duration of an episode of overt HE;
- the model assumes a shorter duration of HE episodes for patients treated with rifaximin + lactulose (3 days) versus lactulose alone (8 days); and
- the assignment of different AR-DRGs for HE hospitalisations to the two treatment groups may be inappropriate given that no data was provided to suggest that patients with treated with rifaximin + lactulose would experience less severe HE requiring hospitalisation compared to those treated with lactulose alone.

The PBAC considered that in the context of the uncertainties raised above, the base incremental cost per QALY over 6 months was high and uncertain.

The PBAC therefore rejected the submission for rifaximin on the basis of high and very uncertain cost effectiveness.

The PBAC also acknowledged and noted the consumer comments on this item.

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 comment.