

Rifaximin: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

September 2016

Abstract

Purpose

To examine the utilisation of rifaximin for hepatic encephalopathy in the 24 months after PBS listing.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Rifaximin was listed on the PBS on 1 December 2013.

Data Source / methodology

The analyses used data from the DUSC database and the Department of Human Services (DHS) supplied prescriptions database.

Key Findings

- The number of PBS/RPBS rifaximin prescriptions supplied per month has increased steadily since its listing in December 2013.
- 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.
- In the first year of listing, the number of rifaximin prescriptions supplied and the government expenditure were lower than predicted. In the second year of listing, prescriptions and government expenditure were close to the estimate.
- The number of prescriptions per patient per year was lower than estimated.

Purpose of analysis

To examine the utilisation of rifaximin for hepatic encephalopathy in the 24 months after PBS listing.

In the context of antimicrobial resistance, DUSC requested a simple 24 month predicted versus actual analysis to facilitate monitoring of rifaximin over time. DUSC considered that the Authority Required listing encourages appropriate use of PBS subsidised rifaximin, but noted that resistance patterns will also be influenced by non-PBS use of rifaximin including compounded product.

Background

Pharmacology¹

Rifaximin is an antibiotic that passes through the gastrointestinal tract and very little is absorbed. It is used to help prevent a condition called hepatic encephalopathy (HE). HE is a disease of the brain that occurs when the liver is not functioning properly. Symptoms are caused by too much ammonia in the blood. Rifaximin works by killing bacteria in the gut that produce ammonia, which means less ammonia is produced therefore less enters the bloodstream. Rifaximin is intended to be used for preventing HE only in those patients where HE is likely to occur again, and where it cannot be managed with other treatments. There is no experience using rifaximin to prevent the recurrence of HE in children or adolescents.

Therapeutic Goods Administration (TGA) approved indications

Rifaximin is TGA registered for preventing the recurrence of HE where other treatments have failed or are contraindicated.

It is also TGA registered, but not PBS-listed, for the treatment of patients (over 12 years of age) with travellers' diarrhoea caused by non-invasive strains of Escherichia coli bacteria.

Dosage and administration

Rifaximin is recommended for patients with repeated episodes of HE despite lactulose therapy. The recommended dose of rifaximin is 550 mg taken orally twice a day, with or without food.²

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

Clinical situation

Treatment of hepatic encephalopathy

Most treatments for HE are aimed at reducing the production of ammonia in the gut, which reduces the amount in the bloodstream. This reduces the neurotoxic effects on the brain and thus the symptoms of HE.³ Ongoing therapy with lactulose is the main treatment used to prevent recurrent HE, or to treat patients with chronic HE.

The PBS restriction for rifaximin for prevention of HE requires that the:

- treatment is in combination with lactulose, if lactulose is tolerated
- patient had prior episodes of HE.

This is consistent with clinical guidance that secondary prevention after an episode of fully symptomatic HE is recommended and the use of rifaximin alone is not supported.⁴

In April 2015, the sponsor of rifaximin, Norgine, announced a real world outcomes study of HE patients in Europe and Australia.⁵ It appears that patients are being recruited for the study in the United Kingdom.⁶

PBS listing details (current as at August 2016)

Table 1: PBS listing of rifaximin

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
10001J	Rifaximin 550 mg tablet, 56	1	5	\$490.25	Xifaxan® Norgine Pty Ltd

Source: the [PBS website](#).

Restriction

Rifaximin is PBS-listed for the prevention of HE. The treatment must be in combination with lactulose, if lactulose is tolerated, and the patient must have had prior episodes of HE. The patient must be treated by a gastroenterologist or hepatologist or in consultation with a gastroenterologist or hepatologist.

A telephone authority approval must be obtained by the prescriber from the Department of Human Services.

For details of the current PBS-listing refer to the [PBS website](#).

Date of listing on PBS

Rifaximin was listed on the PBS on 1 December 2013.

Changes to listing

Since the date of rifaximin listing, there have been formatting changes to the restriction, but no changes to the content. Current PBS listing details are available from the [PBS website](#).

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

At its November 2011 meeting, the PBAC considered a submission for a Restricted Benefit listing of rifaximin for the prevention of a further recurrence or relapse in a patient who has already had an episode of HE. The PBAC rejected the submission on the basis of high and very uncertain cost effectiveness.

For further details refer to the [Public Summary Document](#) from the November 2011 PBAC meeting.

At its July 2012 meeting, the PBAC considered a re-submission for a Restricted Benefit listing, in combination with lactulose, for the prevention of HE in adult patients who have had prior episodes of HE. The PBAC rejected the submission for rifaximin on the basis of high, uncertain, and unacceptable cost effectiveness.

For further details refer to the [Public Summary Document](#) from the July 2012 PBAC meeting.

At its November 2012 meeting, the PBAC considered the re-submission of rifaximin. The PBAC remained concerned regarding the development of antimicrobial resistance associated with the use of rifaximin. The PBAC recommended that clinical advice should be sought on the following issues:

- potential effects of long-term rifaximin use on both individual and population antimicrobial resistance
- impact on hospital antimicrobial resistance
- monitoring requirements should a PBS listing for rifaximin be implemented
- resistance endpoints

The PBAC noted the re-submission's proposal of a retrospective cohort analysis in relation to a managed entry approach for PBS listing of rifaximin. A managed entry approach was considered a possible way forward by the PBAC.

The PBAC agreed 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 would be required to be negotiated in order to manage Government expenditure should PBS listing of rifaximin be achieved.

The decision was deferred. For further details refer to the [Public Summary Document](#) from the November 2012 PBAC meeting.

At its April 2013 meeting, the PBAC considered the re-submission of rifaximin. The PBAC considered that the price offered in the sponsor's pre-PBAC response addressed uncertainties and proposed a price that provided acceptable cost effectiveness for rifaximin. The PBAC considered the advice from the Managed Entry Scheme working group and the sponsor's response and determined that there was no longer a requirement for a managed entry scheme approach.

The PBAC noted the need for prescribing to be managed principally by specialists in this therapeutic area but acknowledged the difficulties for patients with limited access to these specialists. Therefore, the PBAC considered that the restriction should be 'in consultation with' and appropriate specialists (hepatologists and gastroenterologists).

The PBAC recommended the Authority Required PBS listing of rifaximin on the basis of high clinical need, improved clinical benefit over the existing treatments and acceptable cost effectiveness.

For further details refer to the [Public Summary Document](#) from the April 2013 PBAC meeting.

Approach taken to estimate utilisation

The rifaximin submission's estimates for estimating utilisation were based on a three stepped epidemiological approach as follows:

- Step 1: Consider the number of Australian hospital separations for liver diseases;
- Step 2: Consider the evidence on the occurrence of HE among patients with those liver conditions; and
- Step 3: Estimate the number of separations per year attributable to HE, and therefore the number of patients eligible for treatment with rifaximin.

The submission extrapolated hospitalisation data from 2004/5-2007/8 to estimate the number of eligible patients in 2010/11-2015/16. The submission assumed that each patient would have an average of 3.2 hospitalisation episodes per year (doubling of 1.6 events in 6 months as quoted in Leevy & Phillips. (2007)), and 45.2% of patients with HE are hospitalised over 1 year (doubling of 22.6% [hospitalisation rate in placebo arm] at 6 months from RFHE3001).

DUSC (October 2011) considered the estimate of patients treated each year with rifaximin to be uncertain and a likely underestimate. The submission had possibly underestimated the eligible population by underestimating the number of patients experiencing HE events in those hospitalised and the total population including those not hospitalised for HE.

DUSC also noted that the PBS restriction allowed rifaximin use in patients who have experienced one HE event compared to the trial population who had two or more prior episodes of HE. Therefore rifaximin may be prescribed in a larger population of patients with less severe hepatic disease than those included in the trial.

DUSC considered an annual compliance rate of 84.3% to be a likely overestimate. There was also considerable uncertainty as to how rifaximin would be prescribed (intermittently or continuously) and for how long. Despite being indicated for prevention of HE, DUSC considered that it would be conceivable that patients may only take rifaximin when experiencing exacerbations of HE.

The submission estimated that uptake would be 50% in year 1 increasing to 75% in year 5 of listing.

The original (November 2011) and final estimates of use of rifaximin are presented in Table 2.

Table 2: November 2011 submission estimates compared with final agreed estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
November 2011					
Total number of patients treated/year	632	832	1,005	1,191	1,342
Total number of prescriptions/packs	6,393	8,417	10,167	12,048	13,576
Net cost to Government for the drug	\$4,646,634	\$6,117,088	\$7,389,030	\$8,756,552	\$9,866,745
Final agreed estimates					
Total number of patients treated/year	916	1,102	1,301	1,460	1,627
Total number of prescriptions/packs	10,038	12,077	14,258	16,000	17,830
Net cost to Government for the drug	\$4,928,327	\$5,929,056	\$6,999,728	\$7,855,185	\$8,753,687

Source: Final estimates agreed between the Sponsor and the Department

Methods

The DUSC database was used to analyse prescriptions and PBS/RPBS benefits.

The Department of Human Services (DHS) supplied prescriptions database includes data submitted to DHS for payment of a PBS/RPBS subsidy by the Government. This database includes a patient de-identified number that allows supplied prescriptions to be attributed to a particular patient. This allows for patients to be classified as new patients and to identify prior treatments. The DHS database was used for patient level analyses; including initiating and prevalent, prescriber type, time to resupply and length of treatment.

For the patient level analyses, patients initiating to therapy were defined as those who have not been supplied rifaximin since it was PBS-listed in December 2013.

To examine the median number of prescriptions per patient per year and the time to resupply, a cohort of patients first initiating between October 2014 and March 2015 was obtained from the DHS Prescriptions database. This initiation period was selected to allow a maximum follow-up of 12 months to the most recent data available at the time of the report (March 2016). The maximum number of prescriptions and the time between each resupply was derived for each patient over 12 months from the date of initiation.

As these analyses used date of supply prescription data, there may be small differences compared with publicly available DHS Medicare date of processing data.⁷

Results

Analysis of drug utilisation

Overall utilisation

The number of PBS/RPBS rifaximin prescriptions supplied per month has increased steadily since its listing in December 2013 (Figure 1).

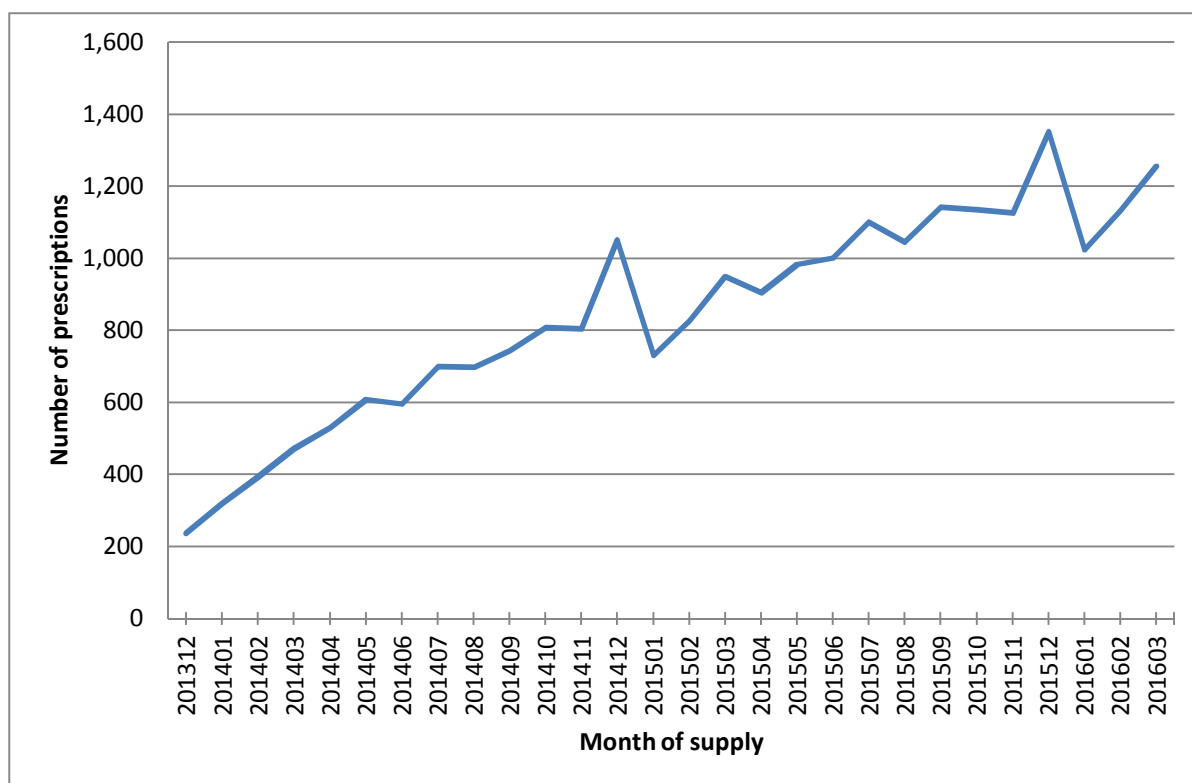


Figure 1: Number of PBS/RPBS rifaximin prescriptions supplied since listing

Prescriptions by date of supply. Source: DUSC database accessed July 2016.

Table 3 shows the number of PBS/RPBS prescriptions for rifaximin supplied by calendar year. From 1 December 2013 to 31 March 2016 there were 23,672 PBS/RPBS prescriptions for rifaximin supplied.

Table 3: Number of PBS/RPBS rifaximin prescriptions supplied

Listing year	Number of prescriptions
Year 1 (Dec 2013 – Nov 2014)	6,909
Year 2 (Dec 2014 – Nov 2015)	11,998

Prescriptions by date of supply. Source: DUSC database accessed July 2016.

Patients initiating and prevalent to rifaximin therapy

Table 4 shows the number of patients supplied rifaximin in the first two years of PBS/RPBS listing.

Table 4: Number of patients initiating and prevalent to rifaximin therapy by listing years

Listing year	New patients (initiators)	Total patients (prevalent)
Year 1 (Dec 2013 – Nov 2014)	1,297	1,297
Year 2 (Dec 2014 – Nov 2015)	1,191	1,977

Rifaximin PBS listed 1 December 2013. Source: DHS supplied prescription database accessed August 2016.

The number of patients supplied rifaximin grew from year 1 to year 2, while the number of new patients each year was similar.

Analysis by prescriber type

When recommending rifaximin for listing, the PBAC noted the need for prescribing to be managed principally by specialists in this therapeutic area, but acknowledged the difficulties for patients with limited access to these specialists. Therefore, the PBAC considered that the restriction should allow prescribing ‘by or in consultation with’ appropriate specialists (hepatologists and gastroenterologists).

For more than half of patients new to rifaximin, their first prescription was written by a general practitioner (Figure 2). There was little difference in the proportion of first prescriptions written by general practitioners and specialists by listing year.

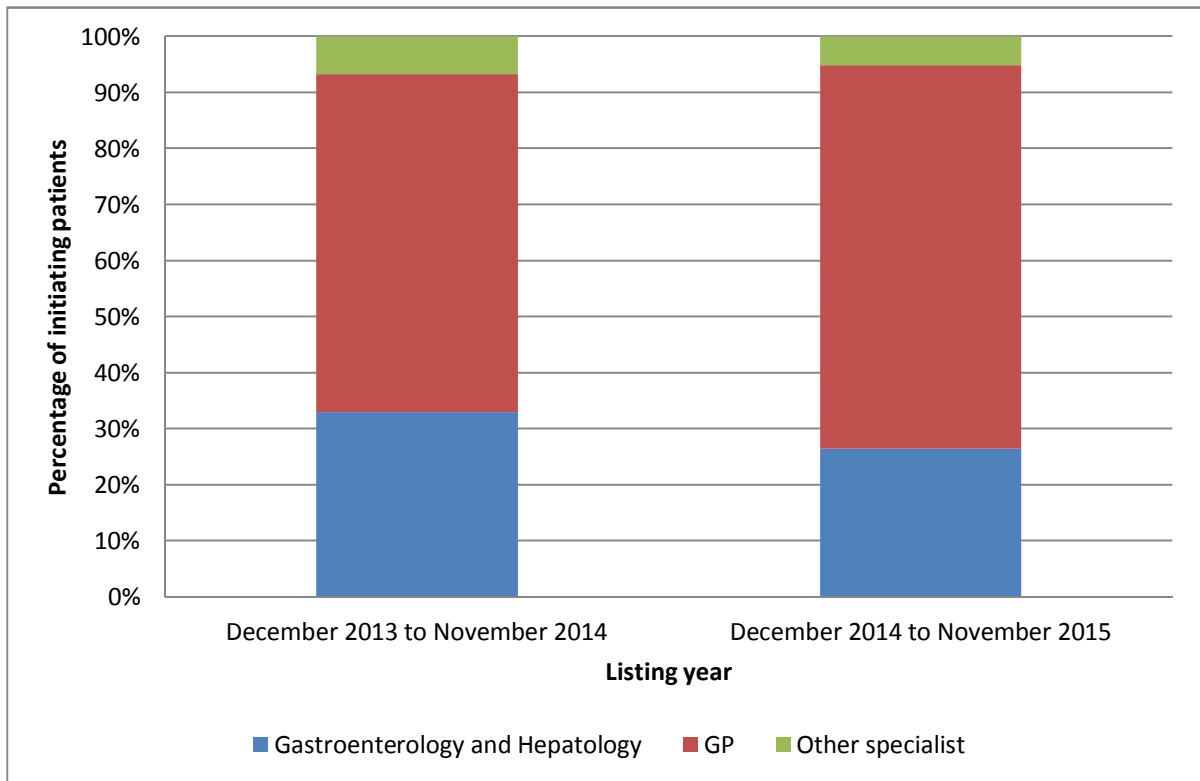


Figure 2: Number of patients initiating rifaximin by prescriber type and listing years
 Rifaximin PBS listed 1 December 2013. Source: DHS supplied prescription database accessed August 2016.

Time to resupply

Figure 3 shows the distribution of time to resupply for a cohort of rifaximin patients who were supplied their first rifaximin prescription between October 2014 and March 2015 inclusive.

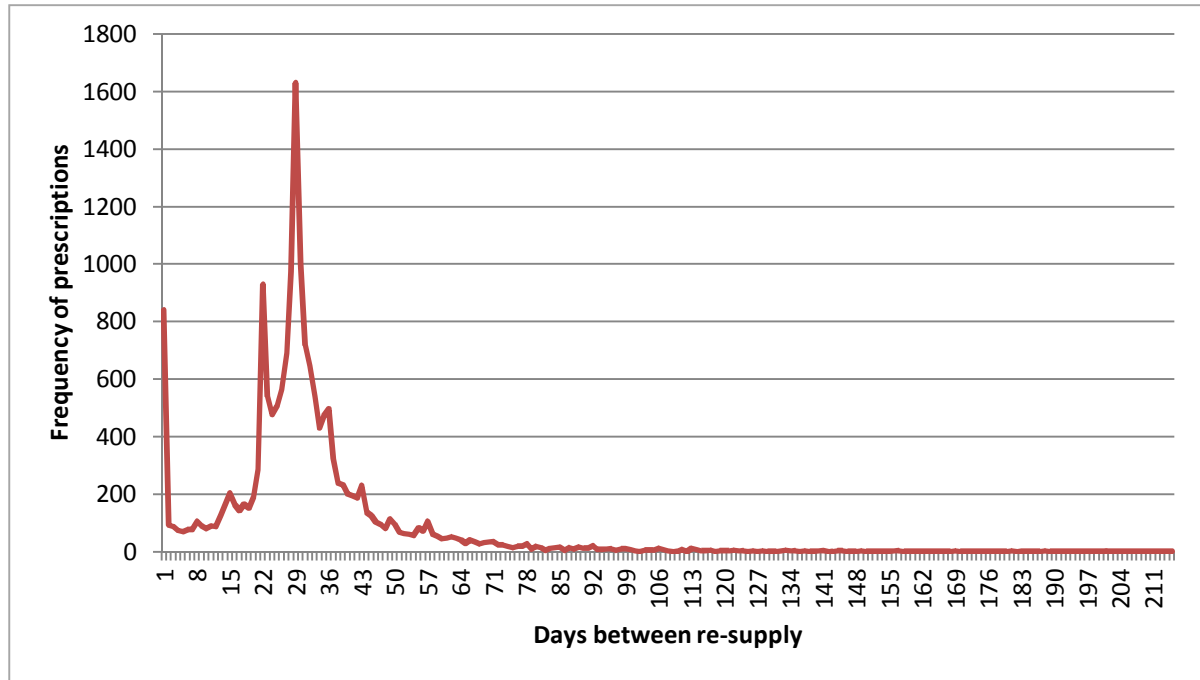


Figure 3: Distribution of time to resupply for patients who were supplied their first rifaximin prescription between October 2014 and March 2015 inclusive

Source: DHS supplied prescription database accessed September 2016.

While there was a peak in re-supply at 28 days, which correlates with the pack size of 56 and recommended dose of twice daily, there was spread evident in the distribution of time to resupply. Of the 18,141 prescriptions supplied in the study period, 6.4% were resupplied in less than five days, 10.6% were resupplied in 5 to 19 days, 60.2% were resupplied in 20 to 35 days and 22.8% were resupplied in 36 or more days.

Prescriptions per patient

Table 5 shows the median and mean number of prescriptions per patient per year for a cohort of patients who were supplied their first PBS/RPBS rifaximin prescription in October 2014 to March 2015 inclusive. Each patient was followed up in the data for 12 months from their date of initiation to rifaximin.

Table 5: Prescriptions per patient per year

Number of patient records in cohort	Mean prescriptions per patient per year	Median prescriptions patient per year	Maximum prescriptions per patient per year
3,362	6	5	26

Note: Based on 551 initiators commencing rifaximin between October 2014 and March 2015.

Analysis of expenditure

Table 6 shows the government expenditure for rifaximin in the first two years of listing.

Table 6: PBS/RPBS benefits for rifaximin

Listing year	PBS/RPBS benefits
Year 1 (Dec 2013 – Nov 2014)	\$3,339,636
Year 2 (Dec 2014 – Nov 2015)	\$5,754,070

Source: DUSC database using date of supply, which may be slightly different to publicly available Medicare Australia date of processing data, accessed July 2016.

It should be noted this analysis is based on date of supply. There may be small differences between these results and those obtained from publicly available Medicare Australia date of processing data.

Analysis of actual versus predicted utilisation

This analysis compares the estimates of utilisation agreed between the sponsor and the department prior to listing. The actual numbers reflect all PBS and RPBS patients, prescriptions and government expenditure for rifaximin.

Table 7: Predicted versus actual numbers of rifaximin patients, prescriptions and benefits

		Year 1 ^a	Year 2 ^b
Patients	Predicted	916	1,102
	Actual	1,297	1,977
	Difference	42%	79%
Prescriptions	Predicted	10,038	12,077
	Actual	6,909	11,998
	Difference	-31%	-1%
PBS/RPBS Benefits	Predicted	\$4,928,327	\$5,929,056
	Actual	\$3,339,636	\$5,754,070
	Difference	-32%	-3%

^a Year 1: December 2013 to November 2014

^b Year 2: December 2014 to November 2015

Source: Patient data from DHS supplied prescription database accessed August 2016; prescription and benefits data from DUSC database accessed July 2016.

In the first year of listing, the number of patients was 42% higher than predicted. However, the number of prescriptions and government expenditure were 31% and 32% lower than predicted, respectively. In the second year of listing, the number of prescriptions and the government expenditure were close to predicted, while the number of patients was 79% higher than predicted. This difference between predicted and actual patients and prescriptions arises from patients receiving fewer prescriptions per year than predicted. The submission estimated that patients would have 10.96 prescriptions per year, but on average patients are having about six prescriptions each year (Table 5).

Discussion

Predicted versus actual use

The number of patients supplied rifaximin was higher than predicted in both year 1 and year 2 of listing. This is consistent with the DUSC consideration of the rifaximin PBAC submission. DUSC thought the submission had possibly underestimated the number of hospitalised patients experiencing HE events and the total population including those not hospitalised for HE. DUSC also considered rifaximin may be prescribed in a larger population of patients with less severe hepatic disease than those included in the trial. The number of treated patients could also be higher than predicted if the uptake rates were underestimated.

While the number of patients supplied rifaximin was higher than predicted, these patients received fewer prescriptions per year than predicted. This is also consistent with the DUSC consideration of the rifaximin PBAC submission. DUSC thought people would have fewer prescriptions per year than estimated by the submission. There was also considerable uncertainty as to whether rifaximin would be prescribed intermittently or continuously and for how long. Despite being indicated for prevention of HE, DUSC considered that it would be conceivable that patients may only take rifaximin when experiencing exacerbations of HE. The time to resupply analysis indicates variable patterns of use. Resupply after 28 or more days could indicate poor adherence and/or intermittent use. There were a number of same day supplies and resupplies within five days, which is inconsistent with expected use and the PBS 20 day supply rule. There is also a small peak of supply at 14 days, which could potentially indicate use of higher doses of rifaximin.

Antimicrobial resistance

The PBAC raised concerns regarding the potential development of antimicrobial resistance (AMR) associated with the use of rifaximin. AMR is critical challenge for health care in Australia and around the world.⁸ AMR occurs when bacteria change to protect themselves from the effects of antibiotics. This means that the antibiotics are no longer effective in destroying or stopping the growth of the bacteria. AMR lessens the effectiveness of antibiotics in fighting infections. This may increase the complexity of treatment and the duration of hospital stay, and place an additional burden on patients, healthcare providers and the healthcare system.

As for all antibiotics, there is a potential for bacteria to develop resistance to rifaximin.⁹ Rifaximin is a member of the rifamycin class of antibiotics. Other rifamycin antibiotics registered for use in Australia include rifampicin and rifabutin.¹⁰ If bacteria become resistant to rifaximin this sometimes makes them resistant to other rifamycin antibiotics (known as cross-resistance).⁹

The PBAC sought clinical advice on the implications of listing rifaximin for AMR. The clinical advice received suggested that the risk of resistance from rifaximin use is real but difficult to quantify.¹¹ Because rifaximin is poorly absorbed, the highest selection pressure for rifamycin resistance from rifaximin is on the bacteria in the gut. Evidence suggests that rifaximin readily selects for resistance to the other rifamycins in staphylococci, Clostridium

difficile and Escherichia coli; which may all be present in the gut.^{12,13,14} Resistance to rifamycins can develop both in the target infectious bacteria and in normal gut bacteria.

There are a number of potential uses for rifaximin in addition to hepatic encephalopathy. Rifaximin is also TGA registered for treatment of traveller's diarrhoea, but this use is not PBS subsidised. A variety of clinical studies are currently investigating use of rifaximin to treat other conditions, for example Crohn disease.^{9,15} Rifaximin is also available in Australia as a compounded product. Private prescription data are not included in this report and data on the extent of use of compounded rifaximin is not available.

Nationally coordinated surveillance of AMR and antimicrobial use is one of the objectives of Australia's National Antimicrobial Resistance Strategy.¹⁶ The Antimicrobial Use and Resistance in Australia (AURA) Surveillance System allows integrated analysis and reporting of antimicrobial use at a national level.⁸ The AURA Surveillance System brings together data from a range of sources, including PBS/RPBS data.

DUSC Consideration

The number of patients supplied rifaximin was higher than predicted in both year 1 and year 2 of listing. DUSC recalled that in its consideration of the rifaximin submission (October 2011 meeting), the committee raised a number of reasons why the number of treated patients was underestimated by the submission:

- underestimated number of hospitalised patients experiencing HE events
- excluded patients with HE who were not hospitalised
- potential use in patients with less severe hepatic disease than those included in the trial
- underestimated uptake rates

DUSC identified that another potential reason for a higher number of patients using rifaximin may be because lactulose is not a very effective treatment option for a disease where there are few treatment options. Further, the mortality rate of liver disease and cirrhosis is quite high so it is possible that rifaximin might be trialled as primary prevention. DUSC also noted that the estimates were based on hospital admissions. The sponsor noted that a patient may have been initiated on rifaximin in hospital but had their first PBS-subsidised prescription written by a GP, and considered this would not have been accounted for in the estimates. However, DUSC noted that the estimates included these patients. 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.

While the number of patients supplied rifaximin was higher than predicted, these patients received fewer prescriptions per year than predicted. 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 time to resupply analysis indicates variable patterns of use. Resupply after 28 or more days could indicate poor adherence or intermittent use. There were a number of same day supplies and resupplies within five days, which is inconsistent with expected use and the PBS 20 day supply rule. There was also a small peak of supply at 14 days, which could potentially indicate use of higher doses of rifaximin. DUSC noted that while the time to resupply analysis showed that most rifaximin prescriptions were resupplied quite quickly, people only received six prescriptions per year on average. DUSC suggested that if future analyses of rifaximin use are conducted, the interpretation would be aided by analysis of how many people were only ever supplied one prescription.

The sponsor stated in their response that with the large number of new patients appearing in both Year 1 and in Year 2 the average number of prescriptions per patient will inevitably be lower than in a stable patient population as patients are not necessarily initiated on therapy at the beginning of each PBS year. DUSC acknowledged that patients would initiate throughout the year and that a half-cycle correction was not included in the final estimates model. However, DUSC also considered that for a condition with limited treatment options, there would be a pool of patients available to start therapy at the date of listing. The sponsor acknowledged the DUSC Secretariat had addressed this by performing a further analysis that followed each patient in a cohort for 12 months from their first prescription.

The purpose of this report included reviewing the use of rifaximin in the context of antimicrobial resistance. DUSC agreed with the clinical advice received by the PBAC that 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. While PBS data can be used to assess the extent of use, it does not provide information on resistance. DUSC noted that the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System allows integrated analysis and reporting of antimicrobial use at a national level. DUSC also noted that there have only been two cases of potential resistance, both unsubstantiated.

There are a number of potential uses for rifaximin in addition to hepatic encephalopathy. DUSC noted that rifaximin could be used to treat traveller's diarrhoea (for which it is registered but not PBS-listed), irritable bowel syndrome and Clostridium difficile infection. DUSC considered that at the current level of use, the HE market is not yet saturated. However, DUSC was concerned that if the use of PBS-subsidised rifaximin continues to grow at the current rate, it will likely not be for the treatment of HE, rather for conditions outside of the restriction. DUSC requested the opportunity to consider if rifaximin use should be reviewed again in 24 months to see if the number of patients treated plateaus as the HE market becomes saturated.

DUSC Actions

DUSC requested that the report, stakeholder response and DUSC minutes be provided to the PBAC.

Context for Analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines. The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines. The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor comments

Norgine Pty Ltd: the sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner. The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee. The context for that

information may have changed since publication. To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report. To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

References

- ¹ Xifaxan® (rifaximin). Australian Approved Consumer Medicine Information. NSW: Norgine Pty Ltd. September 2013. Available from < <https://www.ebs.tga.gov.au> >
- ² Advanced liver disease [revised March 2016]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2016 Mar.
- ³ PBAC public summary document rifaximin November 2011.
<http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-11/pbac-psd-rifaximin-nov11>
- ⁴ Vilstrup H. Amodio P. Bajaj J. Cordoba J. Ferenci P. et al. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *Journal of Hepatology* 2014; 61:642–659.
- ⁵ <http://www.norgine.com/media/press-release/norgine-presents-prosper-study-first-ever-real-world-evidence-study-in-hepatic-encephalopathy-patients-taking-rifaximin-550mg>
- ⁶ <https://clinicaltrials.gov/ct2/show/NCT02488993>
- ⁷ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.
- ⁸ Australian Commission on Safety and Quality in Health Care (ACSQHC). *AURA 2016: first Australian report on antimicrobial use and resistance in human health – summary report*. Sydney: ACSQHC, 2016. ISBN: 978-1-925224-48-1 (online). Accessed from www.safetyandquality.gov.au
- ⁹ Calanni F. Renzulli C. Barbanti M, Viscomi GC. Rifaximin: beyond the traditional antibiotic activity. *The Journal of Antibiotics* 2014; 67:667–670. doi:10.1038/ja.2014.106
- ¹⁰ Product Information and Consumer Medicine Information available from <https://www.ebs.tga.gov.au>
- ¹¹ Professor John Turnidge personal communication to the PBAC Secretary, May 2012
- ¹² Valentin T. Leitner E. Rohn A. Zollner-Schwetz I. Hoenigl M. et al. Rifaximin intake leads to emergence of rifampin-resistant staphylococci. *Journal of Infection* 2011; 62(1):34-38. doi: 10.1016/j.jinf.2010.11.004
- ¹³ Curry SR. Marsh JW. Shutt KA. Muto CA. O’Leary MM. et al. High frequency of rifampin resistance identified in an epidemic *Clostridium difficile* clone from a large teaching hospital. *Clinical Infectious Diseases* 2009; 48(4): 425-429. doi: 10.1086/596315
- ¹⁴ Ruiz J. Mensa L. Pons MJ. Vila J. Gascon J. Development of *Escherichia coli* rifaximin-resistant mutants: frequency of selection and stability. *Journal of Antimicrobial Chemotherapy* 2008; 61:1016–1019. doi:10.1093/jac/dkn078
- ¹⁵ <https://clinicaltrials.gov/ct2/show/NCT00603616>
- ¹⁶ Australian Government Department of Health and Department of Agriculture. Responding to the threat of antimicrobial resistance: Australia’s first national antimicrobial resistance strategy 2015-2019. Accessed from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-amr.htm>