Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

rifaximin 550mg film-coated tablets (Targaxan®) SMC No. (893/13)

Norgine Pharmaceuticals Ltd

09 August 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rifaximin (Targaxan®) is accepted for use within NHS Scotland.

Indication under review: reduction in recurrence of episodes of overt hepatic encephalopathy (HE) in patients ≥18 years of age.

In a double-blind randomised controlled study of six months duration, rifaximin was superior to placebo for the primary outcome of time to first overt breakthrough episode of HE.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

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Indication

Reduction in recurrence of episodes of overt hepatic encephalopathy (HE) in patients ≥18 years of age.

In the pivotal study, 91% of the patients were using concomitant lactulose. Consideration should be given to official guidance on the appropriate use of antibacterial agents

Dosing Information

Rifaximin 550mg orally twice a day. The clinical benefit was established from a controlled study in which patients were treated for six months. Treatment beyond six months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction. Rifaximin can be administered with or without food.

Product availability date

28 January 2013

Summary of evidence on comparative efficacy

Hepatic encephalopathy (HE) is caused by an accumulation of toxins that are normally removed by the liver and is characterised by the following symptoms: deterioration in mental status with psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation and, in severe forms, coma.[1] Rifaximin is an antibiotic, proposed to act by inhibiting the division of urea-deaminating bacteria resulting in reduced production of ammonia and other compounds thought to be important in the pathogenesis of HE.[2]

Evidence of efficacy comes from one phase III, multi-centre, randomised, double-blind, placebo controlled study conducted in US, Canada and Russia and its open-label extension study.[1-4] The double-blind study recruited patients aged ≥18 years with ≥ two episodes of overt HE (Conn score ≥2) associated with hepatic cirrhosis during the previous six months and who were in remission (Conn score 0 or 1) at enrolment. Conn scores were defined as: 0 (no personality or behavioural abnormality); 1 (trivial lack of awareness, euphoria, anxiety, shortened attention span or impairment of ability to add or subtract); 2 (lethargy, disorientation with respect to time, obvious personality change or inappropriate behaviour); 3 (somnolence or semi-stupor, responsiveness to stimuli, confusion, gross disorientation or bizarre behaviour) and 4 (coma). Patients were also required to have a Model for End-Stage Liver Disease (MELD) score ≤25 (range; 6 to 40 with higher scores indicating more severe disease). The following were not counted as previous episodes: episodes of HE precipitated by gastrointestinal haemorrhage requiring transfusion of at least two units of blood, by medication use, by renal failure requiring dialysis, or by injury to the central nervous system.

Patients were randomised equally to receive oral treatment with rifaximin 550mg twice daily (n=140) or placebo (n=159) for six months or until discontinuation due to a breakthrough episode of HE or another reason. Concomitant administration of lactulose was permitted and

the dose could be adjusted as required. Lactulose was taken by 91% of patients in both groups. The mean duration of treatment was 130 days in the rifaximin group and 106 days in the placebo group. Efficacy data were analysed in the intention to treat (ITT) population which included all patients who received at least one dose of study medication. Patients were assessed at the clinic on day 7, 14 and then every two weeks thereafter. Patients were also monitored by telephone during non-clinic weeks.

The primary outcome was the time to first breakthrough episode of overt HE; defined as the time from the first dose of study drug to an increase from a baseline Conn score 0 or 1, to a Conn score of ≥2 or from a baseline Conn score 0, to a Conn score of 1 plus a one unit increase in the asterixis grade. Asterixis (a coarse, myoclonic muscle tremor) was assessed by asking patients to extend their arms with wrists flexed backward and fingers open for 30 seconds or more and was graded as 0 (no tremors); 1 (few flapping motions); 2 (occasional flapping motions); 3 (frequent flapping motions); 4 (almost continuous flapping motions). Breakthrough episodes of overt HE were reported in 22% (31/140) of rifaximin patients and 46% (73/159) of placebo patients; hazard ratio 0.42 (95% confidence interval [CI] 0.28 to 0.64) $p<0.001$. The primary endpoint was evaluated in a number of patient subgroups. The hazard ratio significantly favoured rifaximin for all subgroup analyses except for "MELD score 19 to 24" and "not on lactulose at baseline". There was no significant difference between rifaximin and placebo for these subgroups, which had small patient numbers.

Secondary endpoints included hospitalisation, increase from baseline in Conn score and increase from baseline in asterixis grade. Hospitalisation involving HE was reported for 14% (19/140) of rifaximin patients and 23% (36/159) of placebo patients; hazard ratio 0.50 (95% CI 0.29 to 0.87), $p=0.01$. Results of change from baseline in Conn score and asterixis were consistent with the results from the primary efficacy endpoint.[2]

The chronic liver disease questionnaire (CLDQ) was used to assess health related quality of life (HRQL) in a subgroup (n=219) of patients in the pivotal study, as the CLDQ is not validated in Russian.[3] The CLDQ includes 29 items in six domains: abdominal symptoms; fatigue; systemic symptoms; activity; emotional function; and worry. Patients rank each question on a 7-point scale (higher scores indicate better HRQL) and data are presented by domain and overall score. The CLDQ was used in 101 patients in the rifaximin group and 118 in the placebo group. The mean CLDQ overall score at baseline was 4.1 in the rifaximin group and 4.2 in the placebo group. At six months, the time weighted averages for the six domain scores and the overall score were significantly higher in the rifaximin than placebo group.

A multi-centre, open-label extension study (published in abstract form only) recruited 322 patients who had previously participated in the double-blind study (70 rifaximin- and 82 placebo-treated patients) or were new patients (n=170) with at least one verifiable HE episode within 12 months prior to screening.[2,4] Patients from the double-blind study who had experienced a HE episode or symptoms were eligible for the open-label study only if the investigator and patient did not perceive the study medication as a possible cause of the HE episode or symptoms. Patients were treated with open-label rifaximin for 24 months or until close of study, and were permitted to continue with rifaximin if they experienced an overt HE episode. The proportion of patients who were administered concomitant lactulose was 88%. The long-term breakthrough HE event rates (event per person exposure years) were 0.3 (for the placebo patients who crossed over [n=82]); 0.4 (for patients new to rifaximin [n=252]) and 0.24 (for the patients continuing on rifaximin [n=70]). The proportion of patients with at least one breakthrough overt HE episode during the course of the study was 42% (135/322). Of the 135 patients, 64 had one breakthrough, 29 had two breakthroughs and 42 had ≥3 breakthroughs.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the pivotal study similar proportions of patients reported adverse events in the rifaximin group (80% [112/140]) and the placebo group (80% [127/159]). The following adverse events (≥10% incidence in any group) were reported for rifaximin and placebo respectively: nausea (14% versus 13%); diarrhoea (11% versus 13%); fatigue (12% versus 11%); peripheral oedema (15% versus 8.2%); ascites (11% versus 9.4%); dizziness (13% versus 8.2%); and headache (10% versus 11%). Serious adverse events in rifaximin versus placebo groups respectively and reported in ≥2% of patients in either group included: anaemia (four versus no patients), ascites (four patients each), oesophageal varices (four versus two), pneumonia (four versus one), vomiting (three versus none), generalised oedema (three versus two), hepatic cirrhosis (three versus six), cellulitis (three versus two) and acute renal failure (two versus four).[1]

Clostridium difficile infection was reported in two patients in the rifaximin group and none on placebo. Both patients had several risk factors for infection with *Clostridium difficile*, were treated concurrently for the infection and fully recovered.[1]

There were 10 deaths in the rifaximin group and 11 deaths in the placebo groups, and most deaths were associated with disease progression including hepatic cirrhosis, decompensated cirrhosis, hepatic failure, alcoholic cirrhosis or end-stage liver disease (five deaths versus five deaths); oesophageal varices or haemorrhage from oesophageal varices (three deaths versus two deaths).[2]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

In the pivotal, double-blind study, rifaximin was superior to placebo for the primary outcome of time to first overt breakthrough episode of HE. Results of the secondary outcomes were supportive of the primary outcome. In the open-label extension study, HE event rates (events per person exposure years) of 0.24 to 0.40 (depending on previous treatment) were observed.

However, the studies have some limitations. Patients in the double-blind study were discontinued from study treatment when they experienced an overt breakthrough HE episode. Therefore, it is not possible to evaluate the incidence of breakthrough over time in this study. In the open-label extension study, continued treatment was permitted. Another limitation is that the majority of patients had a MELD score ≤18 with only approximately 9% of patients having a higher score. Therefore, there are limited efficacy data in patients with more severe disease. Systemic exposure to rifaximin increases with severity of liver impairment.[2] The summary of product characteristics (SPC) for rifaximin notes that it should be used with caution in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD score >25.[5]

There are no comparative efficacy data beyond a treatment duration of six months. The SPC notes that "Treatment beyond six months should take into consideration the individual balance

between benefits and risks, including those associated with the progression of hepatic dysfunction".

Overt HE episodes are debilitating, often result in hospitalisation and their increased frequency and severity is associated with increased mortality. The availability of rifaximin would provide patients with a treatment for reducing the recurrence of HE episodes, where there are currently limited treatment options, and no national guidance. Clinical experts consulted by SMC considered that there was unmet need. They reported the use of lactulose and noted that off-label neomycin is not used routinely due to ototoxicity and nephrotoxicity with long-term use. Clinical experts considered that rifaximin would be used in addition to lactulose in patients who are not sufficiently controlled on lactulose alone.

As with most antibiotics, there is a risk of *Clostridium difficile* infection with rifaximin treatment and in the pivotal study this was reported in two patients, although other risk factors were also present in both patients. Furthermore, resistance may be an issue with long-term use. However, resistant strains that developed in normal intestinal bacterial flora following repeated rifaximin exposure disappeared following treatment discontinuation.[5]

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The company submitted a cost-utility analysis based on the main clinical study and comparing rifaximin in addition to lactulose with lactulose alone.

A Markov model was used, consisting of three states: alive and in remission, alive and with overt disease, and dead. The model had a 5-year time horizon.

Patients moved between these states based on probabilities. These were taken by fitting a parametric curve to combined data on time to first event from the main clinical study and the open label follow-up study. For second and subsequent events, the following assumptions were used:

1. The risk associated with experiencing a subsequent overt HE episode is independent of the risk of preceding episode(s).
2. The risk of subsequent overt HE episodes is independent of time spent in the remission health state.
3. The risk of subsequent overt HE episodes is assumed to be constant over time and the same risk reduction for the first breakthrough episode is applied to subsequent episodes.

Mortality data were taken from two published studies and gave rates by Conn scores.

Utility values for the states were taken from a study commissioned by the company using time-trade-off to value descriptions of the symptoms associated with each Conn score in members of the UK public.

Resource use included the costs of the medicine and of routine care in terms of out-patient clinics and hospital admissions for breakthrough events (the chances of hospital admission when a breakthrough occurred) which were taken from the main clinical study. Transplant costs

were not included since there is no evidence of an impact of the medicine on rates of this intervention. Data on number of clinic visits and length of hospital stay were taken from expert opinion but in sensitivity analyses these were not key drivers of the results.

While the doses of the medicine in the economic model reflected the clinical studies, the assumption about duration was that patients took the medicine until they died (or until the end of the model after 5 years) with 100% compliance; this was varied in the sensitivity analysis, but only to 84% compliance.

The main result in the submission was that adding rifaximin to lactulose was estimated to add £4,272 to lifetime cost and to gain 0.19 quality-adjusted life-years (QALYs) (1.22 versus 1.03 with lactulose alone). The net cost per QALY gained was £23,314. However, in a scenario analysis the compliance rate was varied: in the base case it was 100% but when it was set to 84%, the level in the main clinical study, the cost per QALY fell to just over £20k. In practice, the compliance rate may be even lower but the scenario analysis seems a better representation than the base case.

In other sensitivity analyses, assumptions about the extrapolation and mortality rate were shown to be important. The probabilistic sensitivity analysis submitted suggested a very high probability that the cost per QALY lay in the range £20k to £30k.

The analysis was based on the pivotal study and included a realistic treatment comparator. It was helpful that the company chose to commission the utility survey rather than using values from the literature that may be less relevant.

The company provided further justification for their extrapolation and for the mortality rates used in terms of applicability to Scotland; these reduced the uncertainty regarding these points.

The main issue was with the treatment pathway used in the economic model. It was assumed that once a patient started on rifaximin (in addition to lactulose) or lactulose alone, then they continued on treatment with 100% compliance until they died (or the end of the model). A sensitivity analysis on compliance reduced the rate to 84%, which was some help, but still assumed all patients would be on treatment but that they would only take 84% of the pills dispensed. No attempt was made to model discontinuation either on grounds of ineffective treatment, side-effects or patient preference and no subsequent lines of treatment were considered. There was also concern that the risk of subsequent events was modelled as being independent of the risk of previous events; this was felt to be unrealistic based on clinical experience.

However, despite these issues, the economic case was considered to have been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Lactulose.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 6 months (£)
Rifaximin*	**550mg orally twice daily**	**1,685**
Lactulose	30mL to 50mL orally three times daily	66 to 110

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMs on 14 May 2013 and eVadis on 10 June 2013.
* In the double-blind study 91% of patients were also taking lactulose.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 1,102 in all 5 years, with an estimated uptake rate of 8% in year 1 and 40% in year 5.

The gross impact on the medicines budget was estimated to be £298k in year 1 and £1.489m in year 5. As no other drugs were assumed to be displaced, the net medicines budget impact is expected to be £298k in year 1 and £1.489m in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362 (12):1071-81.
2. Medicines and Healthcare Products Regulatory Agency (MHRA). Public assessment report for rifaximin, decentralised procedure. UK/H/4662/001/DC. [last accessed 14 May 2013]
3. Sanyal A, Younossi ZM, Bass NM et al. Randomised clinical trial; rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy- a double-blind placebo-controlled study. Alimen Pharmacol Ther. 2011; 34: 853-61
4. Mullen KD, Sanyal AJ, Bass NM, et al. The long term efficacy and safety of Rifaximin in the maintenance of remission from overt hepatic encephalopathy in cirrhotic patients. Digestive Disease Week. 2012 abstract no 168
5. Norgine Pharmaceuticals Ltd. Summary of product characteristics for rifaximin (Targaxan®). Last revised January 2013.

This assessment is based on data submitted by the applicant company up to and including 12 July 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.