National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Rifaximin for maintaining remission from episodes of hepatic encephalopathy [ID496]

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **[08 May 2013]** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Title of ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The current title of the report is: "The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy"	Norgine requests that this is amended to: 'The clinical and cost-effectiveness of rifaximin 550mg for the reduction in recurrence of episodes of overt hepatic encephalopathy in adults ≥18 years of age.'	The altered title is more appropriate as it accurately reflects the indication for rifaximin 550mg (SmPC).	We do not agree. The manufacturer request would suit the purpose of providing more detail on the indication of rifaximin. However the ERG did not believe this to be a factual error, consisting on a broader description of rifaximin indication instead.

Issue 2 Comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6. Section 1.1 and throughout the remainder of the document 'The comparator used was placebo with concomitant lactulose.'	Norgine requests this is amended to: 'The comparator used was placebo'	Throughout the submission rifaximin plus standard of care is termed 'rifaximin' and placebo plus standard of care is termed 'placebo'. 'Standard of care' is defined as 91% of patients on a variable dose of lactulose and 9% not on lactulose.	Agree

Issue 3 Intervention

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6 (Section 1.1), 8 and 9 Section 1.5 on Key Issues. The report states: "…if the indication of rifaximin is meant for patients taking rifaximin alone, then the economic model developed by Norgine for this submission is not sufficient to inform the overall costs and benefits of the drug."	Norgine requests the removal of this bullet point: "…if the indication of rifaximin is meant for patients taking rifaximin alone, then the economic model developed by Norgine for this submission is not sufficient to inform the overall costs and benefits of the drug."	Whilst there is no requirement for the administration of other therapies with rifaximin (SmPC), the submission compares rifaximin plus the current standard of care to placebo plus current standard of care. 'Standard of care' is defined as 91% of patients on a variable dose of lactulose and 9% not on lactulose. The evidence for this is derived from the rifaximin pivotal study where approximately 91% of patients received concomitant lactulose in both the rifaximin and placebo arms. This closely reflects future clinical practice in the UK where, in the majority of cases, rifaximin (for the reduction of recurrence of HE episodes) will most likely be prescribed concomitantly with lactulose. This has been verified with practicing clinicians. Therefore, the evidence provided is appropriate.	The ERG understands that prescribing rifaximin concomitantly with lactulose reflects current practice and therefore the approach taken is appropriate for the economic model. What the ERG wishes to point out with the statement in question is that the economic model developed by Norgine is only suited to evaluate the costs and benefits of rifaximin when taken together with lactulose (and not those associated with rifaximin alone).

Issue 4 Justification for extrapolation assumption

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53 and page 56, Section	Norgine requests the current	Norgine supplied as thorough a justification	We do not agree. Some of the

5.2.3 on the data extrapolation process. Page 63, Section 5.3.1. on one-way analysis The wording used by the ERG in these sections imply that no attempt has been made to justify the use of specific distributions within the submission.	wording in the report should be amended to highlight the fact that the justification for the lognormal distribution was provided in the response to the ERG clarification questions.	for the use of specific distributions via the response to ERG clarification questions. Norgine also provided additional analyses within the clarification process. The choice of distributions within the model was justified based on: 1) Visual inspection 2) AIC/BIC criteria 3) KOL opinion	justifications still fell short in assessing the best model fit.

Issue 5 Scenario Analysis on Neomycin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69 and page 73, Section 6.1.3. on additional work carried out by the ERG. The ERG presents a scenario comparing rifaximin with neomycin in this section.	Norgine requests the removal of this scenario analysis.	In Norgine's view, the presentation of this scenario is unjustified. The results are highly uncertain and misleading. There is insufficient data for inclusion of neomycin as a comparator, and its exclusion as evidence in this appraisal has previously been outlined by Norgine in response to the ERG clarification questions. The ERG acknowledged these reasons and found plausibility in some of them. Only one trial (Miglio et al, 1997) was identified that compared rifaximin to neomycin. This study found rifaximin and neomycin were equally effective in reducing HE grade after 30 days. It is our view that extrapolation of results from 30	We do not agree. The ERG clearly acknowledges this to be an exploratory analysis.Tthe ERG sees value in presenting such analysis as although we find plausibility in some of the reasons provided for the decision of excluding neomycin, Miglio et al, 1997 found rifaximin and neomycin to be equally effective in reducing HE grade after 30 days.

		days to a five year time horizon is wholly inappropriate. Furthermore, this scenario analysis makes an assumption that the benefits and risks of rifaximin and neomycin are equal. As these assumptions are unfounded, we request that the scenario analysis be removed.	

Issue 6 Unlicensed use of neomycin in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
However, our clinical advisor indicated that although in some patients neomycin is not as well tolerated as rifaximin, it is sometimes used in clinical practice (especially in patients that will not undergo liver transplant (2.2. page 10)	Please insert the following text after the statement '…. (especially in patients that will not undergo liver transplant)'. 'Please note the licensed indication for neomycin (Nivemycin) includes "…may be useful in the treatment of impending hepatic coma, including portal systemic encephalopathy. Prolonged therapy with neomycin is associated with ototoxicity and nephrotoxicity particularly in patients with a degree of renal failure (Neomycin SmPC)'	The statement '….sometimes used in clinical practice' is ambiguous. This could be interpreted as anything from acute treatment to secondary prevention. Whilst we agree that neomycin may have sometimes been used in clinical practice, the licensed indication for neomycin (Nivemycin) includes "…may be useful in the treatment of impending hepatic coma, including portal systemic encephalopathy", it is not well tolerated and carries a number of warnings on long term use on its SMPC. Norgine interprets this as an indication for the acute treatment of hepatic coma and not for prevention of recurrence of HE. Thus, the statement needs to be adjusted to provide clarity and add the specific warnings for prolonged use of neomycin.	We do not agree. The point of the ERG was to make note that neomycin is still prescribed in some occasions. The ERG did not believe this to be a factual error, consisting on a broader description of neomycin indication than the one the manufacturer is providing.

		As part of the new GMC guidance 2013, doctors should only prescribe medicines outside of their licence where no licensed medication is available. TARGAXAN is now licensed for the reduction in recurrence of overt hepatic episodes in patient's ≥18 years old.	

Issue 7 Similarities / Differences between Rifaximin and Neomycin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1. Page 12. **Reason for excluding neomycin as comparator** / **Critique based on clinical expert opinion**	• Norgine request that the ERG deletes the following statement: 'Neomycin is an antibiotic that works through the same process as rifaximin'. • In addition, please update the following as per issue 6: 'Although in some patients neomycin is not as well tolerated as rifaximin, it is sometimes used in clinical practice (especially in patients that will not undergo liver transplant).'	Below are the differences between neomycin and rifaximin that contradict the comment that the two drugs work through the same process: **Mechanism of Action**: <u>Neomycin</u> Neomycin is an aminoglycoside antibiotic. Neomycin acts by binding to polysomes, inhibiting protein synthesis and generating errors in the transcription of the genetic code. <u>Rifaximin</u> Rifaximin is an antibacterial dug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA	We do not agree. The ERG did not believe this to be a factual error. The ERG provided a broader description of neomycin classification than the one the manufacturer is suggesting.

Neomycin is not licensed for the indication.	Neomycin is an antibiotic that works through the same process as rifaximin. Although in some patients neomycin is not as well tolerated as rifaximin, it is sometimes used in clinical practice (especially in patients that will not undergo liver transplant).		synthesis. **Spectrum of activity** <u>Neomycin</u> Neomycin has a broad spectrum of activity that includes most Gram-negative aerobes, except Pseudomonas aeruginosa, and also possesses anti-staphylococcal activity. <u>Rifaximin</u> Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species. Rifaximin may inhibit the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy. **Pharmacokinetics** <u>Neomycin</u> Absorption: ~ 3% of an oral dose of neomycin is absorbed. Elimination: Neomycin is rapidly excreted by the kidneys in the unchanged form.	

		Rifaximin Absorption: Pharmacokinetic studies have demonstrated that after oral administration rifaximin in the polymorph α form is poorly absorbed (less than 1%). Elimination: The urinary recovery of 14C-rifaximin does not exceed 0.4% of the administered dose. **Licensed Indication** Neomycin Nivemycin (Neomycin sulphate BP) is indicated for pre-operative sterilisation of the bowel and may be useful in the treatment of impending hepatic coma, including portal systemic encephalopathy. Rifaximin Rifaximin is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age	

Issue 8 Long-term safety

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Reason for excluding neomycin as comparator: *Neomycin is not commonly used in clinical practice for long-term prevention of HE recurrence. The neomycin summary of product characteristics (SPC) contains warnings against long-term use.* **Critique based on clinical expert opinion**: There are no equivalent studies assessing the long-term use of rifaximin and its side effects. Therefore similar warnings against long-term use of rifaximin cannot be ruled out.	Norgine requests removal of this statement: 'There are no equivalent studies assessing the long-term use of rifaximin and its side effects. Therefore similar warnings against long-term use of rifaximin cannot be ruled out.'	The SmPC for neomycin does not give details of any long-term safety study. Therefore, Norgine believes the statement is not evidence based and should be removed. Rifaximin on the other does have published long-term safety data as follows: In the long term study (24 months): Rifaximin had a favourable safety profile in patients with chronic liver disease (Mullen et al Abstract, 2012 and CSR RFHE3002) In addition the RMS Day 210 Final Assessment report states that: "Post-marketing pharmacovigilance surveillance has not raised any demonstrable safety concerns" for rifaximin in relation to its approval for the treatment of HE in 10 countries, and as adjunctive therapy for the treatment of hyperammonemia in 12 countries worldwide. The Risk-Benefit Assessment in the RMS Day 210 Final Assessment report is as follows: "The use of rifaximin for the reduction of recurrence of episodes of overt HE is supported by a well-conducted, placebo-controlled phase 3 study, which demonstrated convincing evidence of reduced episodes in the	Agree.

		rifaximin group compared to the placebo group. This primary endpoint was also supported by sensitivity analyses and sub group analyses. A long-term study for 24 months showed the efficacy was maintained over this duration. There is a high incidence of side effects seen in the clinical trials. These have been mentioned under appropriate sections of the SPC as well as covered in the risk management plan. There are limited effective options available for the treatment of HE. Rifaximin has been approved and used in a number of European countries and US. Published literature also supports the use of rifaximin in HE. Therefore based on the submitted data the benefit-risk ratio is considered favourable." Based on all the information provided above there are no SMPC warnings relating to the long term use of rifaximin, whereas the neomycin SMPC clearly states: "The absorption of neomycin is poor from the alimentary tract, with about 97% of an orally administered dose being excreted unchanged in the faeces. Impaired G.I. motility however may increase absorption of the drug and it is therefore possible, as with other broad spectrum antibiotics that prolonged therapy could result in ototoxicity and nephrotoxicity, particularly	

		in patients with a degree of renal failure. In such patients, and in infants and the elderly, it is generally desirable to determine dosage requirements of aminoglycosides by individual monitoring. Some authorities consider that monitoring is also important in obese patients and those with cystic fibrosis. Impaired hepatic function or auditory function, bacteraemia, fever, and possibly exposure to loud noises have been reported to increase the risk of ototoxicity, while volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity. Regular assessment of auditory, vestibular and renal function is particularly necessary in patients with additional risk factors. When used as an adjunct in the management of hepatic coma, care should be taken that administration is of the minimal period necessary, since prolonged exposure to the drug may result in malabsorption”.	

Issue 9 Patient Characteristics

Description of problem		Description of proposed amendment	Justification for amendment	ERG response
Reason for excluding neomycin as comparator	**Critique based on clinical expert opinion**	Please remove the following statement: 'As stated previously however, neomycin is sometimes is used in patients with similar characteristics as those that would be indicated rifaximin.'	There are no reported or published neomycin studies in the licensed indication for rifaximin. Hence, there is no evidence to support this statement.	We do not agree. The point of the ERG was to make note that neomycin is still prescribed in some occasions as an alternative to rifaximin.

	There is no evidence for the efficacy of neomycin or neomycin and lactulose in combination in this indication.	A study (Miglio et al, 1997) comparing the effectiveness of rifaximin and neomycin was identified. Norgine considered inappropriate to use this study to inform a comparison of neomycin with rifaximin due to differences in the patient population, treatment regimens and outcomes used in their main effectiveness study (RFHE3001). As stated previously however, neomycin is sometimes is used in patients with similar characteristics as those that would be indicated rifaximin.			

(please cut and paste further tables as necessary)